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(22) International Filing Date: 7 May 1993 (07.05.93)		(75) Inventors/Applicants (for US only) : MILLER, Timothy, J. [US/US]; 102 Crestside Way, Malvern, PA 19355 (US). KLEPFER, Sharon [US/US]; 113 Lindbergh Avenue, Broomall, PA 19008 (US). REED, Albert, Paul [US/US]; 117 Baker Circle, Exton, PA 19341 (US). JONES, Elaine, V. [US/US]; 1217 Andover Road, Wynnewood, PA 19096 (US).	
(30) Priority data: 07/880,194 8 May 1992 (08.05.92) US		(74) Agents: SCHRECK, Patricia, A. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	
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(54) Title: CANINE CORONAVIRUS S GENE AND USES THEREFOR

(57) Abstract

The present invention provides the amino acid and nucleotide sequences of a CCV spike gene, and compositions containing one or more fragments of the spike gene for prophylaxis, diagnostic, and treatment of CCV infections.

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CANINE CORONAVIRUS S GENE AND USES THEREFOR

Cross-Reference to Related Application

5 This is a continuation-in-part of U.S. Patent Application Serial Ser. No. 07/880,194, filed May 8, 1992, which is a continuation-in-part of U.S. Patent Application Ser. No. 07/698,927, filed May 13, 1991, which is a continuation-in-part of U.S. Patent Application Ser. No. 07/613,066, filed November 14, 1990.

10

Field of the Invention

15 The present invention relates generally to canine coronavirus infections, and specifically to proteins useful in prophylaxis, therapy, and diagnosis of these infections in canines.

15

Background of the Invention

20 The coronaviruses are a large family of mammalian and avian pathogens which were first described in 1968. They are the causative agents of several diseases including encephalitis, hepatitis, peritonitis and gastroenteritis. Enteric coronaviruses have been detected in the feces of man, pigs, calves, cats, mice, chickens and dogs.

20

25 Canine coronavirus (CCV) enteritis was first isolated from dogs suffering an acute gastroenteritis, as reported by Binn et al., Proc. 78th Ann. Mtg. U.S. Animal Health Assoc., Roanoke VA, pp. 359-366 (1974). The disease became prevalent during the 1970s. CCV gastroenteritis appears to be primarily transmitted through fecal contamination from infected dogs via the oral route,

leading ultimately to replication of the virus in the epithelial cells of the small intestine. Virus can be recovered from the feces of an infected dog between 3 and 14 days after infection.

5 CCV gastroenteritis is characterized by a mild depression, anorexia and loose stool from which the dog usually recovers. The onset of the disease is often sudden, accompanied by such symptoms as diarrhea, vomiting, excreted blood in stools, and dehydration. Deaths have
10 occurred within as little as 24 to 36 hours after onset of clinical signs. Most dogs appear afebrile but elevated body temperature is seen in some cases. Often CCV will occur with a canine parvovirus infection and this coinfection can be fatal.

15 Serologically the disease is closely related to transmissible gastroenteritis virus of swine (TGEV). Although canine coronavirus does not infect pigs, transmissible gastroenteritis virus produces a subclinical infection in dogs. However, unlike the feline infectious peritonitis coronavirus (FIPV), previous exposure to CCV
20 does not predispose dogs to enhanced disease; and antigen-antibody complexes, if formed, are not associated with disease pathology.

25 There remains a need in the art for compositions useful in diagnosing, treating and preventing infections with canine coronaviruses.

Summary of the Invention

30 In one aspect the present invention provides the complete nucleotide sequence of the CCV S gene, strain 1-71, SEQ ID NO:1. The S gene or fragments thereof may be useful in diagnostic compositions for CCV infection.

35 In another aspect the present invention provides a CCV S (or spike) protein characterized by the amino acid sequence of a CCV S protein, SEQ ID NO:2, and peptide fragments thereof. These proteins may be optionally fused or linked to other fusion proteins or molecules.

Thus, in another aspect, the present invention provides a vaccine composition containing an effective immunogenic amount of at least one CCV S protein or an immunogenic fragment thereof.

5 In still another aspect, the invention provides a method of vaccinating an animal against infection with a coronavirus by administering an effective amount of a vaccine composition of this invention.

10 In yet a further aspect, the present invention provides a pharmaceutical composition for the treatment of CCV infection comprising a therapeutically effective amount of a CCV S peptide or protein of the invention and a pharmaceutically effective carrier.

15 Still another aspect of this invention is an antibody directed to CCV, which antibody is capable of distinguishing between CCV and other canine viruses. These antibodies may also be employed as diagnostic or therapeutic reagents.

20 In yet another aspect, a diagnostic reagent of the present invention comprises a CCV S protein or fragment thereof. In another aspect, the present invention provides a diagnostic reagent which comprises a nucleotide sequence which encodes a CCV S protein or fragment of the invention, and/or a nucleotide sequence which flanks the coding 25 region, or fragments thereof. These protein and nucleotide sequences are optionally associated with detectable labels. Such diagnostic reagents may be used to assay for the presence of CCV in dogs using standard assay formats and can form components of a diagnostic kit.

30 In a further aspect, the invention provides a method of using a diagnostic reagent of this invention to identify dogs which are uninfected or which have been previously exposed to CCV. The diagnostic method can differentiate exposure to CCV from exposure to other

related coronaviruses, allow the identification of dogs which have been vaccinated against these diseases, and allow one to distinguish between different strains of CCV, or to identify dogs at advanced stages of CCV infection.

5 In yet a further aspect, the invention provides a method for the production of a recombinant CCV protein comprising culturing a selected host cell, e.g., a mammalian cell or viral vector, transformed with a DNA sequence encoding a selected CCV S protein or fragment thereof in operative association with regulatory sequences capable of regulating the expression of said protein.

10 Another aspect of the invention is a recombinant DNA molecule comprising a DNA sequence coding for a selected portion of a canine coronavirus S protein, the DNA sequences in operative association with regulatory sequences capable of directing the expression thereof in host cells.

15 20 Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

Detailed Description of the Invention

25 The present invention provides novel isolated canine coronavirus (CCV) S proteins and fragments thereof, as well as isolated nucleotide sequences encoding the proteins or fragments. These proteins and fragments are useful for diagnostic, vaccinal and therapeutic compositions as well as methods for using these compositions in the diagnosis, prophylaxis and treatment of CCV-related and other coronavirus-related conditions.

I. Definitions

30 As defined herein, an amino acid fragment is any amino acid sequence from at least about 8 amino acids in length up to about the full-length CCV S gene protein. A nucleotide fragment defines a nucleotide sequence which

encodes from at least about 8 amino acids in length up to about the full-length CCV S gene protein.

5 The term "region" refers to all or a portion of a gene or protein, which may contain one or more fragments as defined above.

10 The term "immunogenic" refers to any S gene protein or fragment thereof, any molecule, protein, peptide, carbohydrate, virus, region or portion thereof which is capable of eliciting a protective immune response in a host, e.g., an animal, into which it is introduced.

The term "antigenic" refers only to the ability of a molecule, protein, peptide, carbohydrate, virus, region or portion thereof to elicit antibody formation in a host (not necessarily protective).

15 As used herein, the term "epitope" refers to a region of a protein which is involved in its immunogenicity, and can include regions which induce B cell and/or T cell responses.

20 As used herein, the term "B cell site or T cell site" defines a region of the protein which is a site for B cell or T cell binding. Preferably this term refers to sites which are involved in the immunogenicity of the protein.

II. Sources of CCV Sequences

25 The examples below specifically refer to newly identified spike gene sequences from canine coronavirus (CCV) strain 1-71. This strain is deposited with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland under Accession No. VR-809. 30 Particularly disclosed are nucleotide and amino acid sequences, SEQ ID NO:1 and 2, respectively, of the CCV S gene.

The present invention is not limited to the particular CCV strain employed in the examples. Other CCV strains have been described, e.g., strain CCV-TN449 [ATCC 2068]. Utilizing the teachings of this invention, analogous fragments of other canine coronavirus strains can be identified and used in the compositions of this invention.

5 **III. CCV Nucleotide and Amino Acid Sequences of the Invention.**

10 The inventors have identified and selected nucleotide and protein sequences of CCV strain 1-71 which have been determined to be of interest for use as vaccinal, therapeutic and/or diagnostic compositions. For example, selected peptide and nucleotide sequences present primarily in the variable N terminal region of the CCV S protein and gene are characterized by representing areas of homology between FIPV, TGEV, feline enteric coronavirus (FECV) and other coronavirus strains.

15

20 Peptide fragments obtained from this heterogeneous N terminal of the S protein are useful fragments for diagnostic compositions and kits for distinguishing between infection with CCV strain 1-71 from other CCV infections, and for distinguishing between infection with CCV and other coronavirus identified above in a vaccinated or infected dog, as well as for use in vaccine and therapeutic agents.

25

30 Additionally, the amino terminal sequences of CCV S protein include peptide sequences which are B cell sites and thus useful in vaccinal or therapeutic compositions, or for generating antibodies to CCV, in assays for the detection of CCV antibodies in dogs.

In addition, certain peptide fragments of the CCV S protein are believed to represent T cell sites, and thus are useful in vaccinal or therapeutic compositions.

Other suitable CCV amino acid regions for pharmaceutical or diagnostic use are located within other regions of the CCV S protein SEQ ID NO: 2. These amino acid and nucleotide fragments of the CCV S protein and its nucleotide sequence discussed above are specifically reported below in Tables I and II. Table II also reports the respective homologies of certain of these desired fragments to wild-type FIPV, i.e., FIPV WSU 1146. The CCV S nucleotide fragments in Tables I and II can be useful for diagnostic probes, PCR primers, or for use in recombinant production of relevant S protein fragments for use in therapeutic or vaccinal compositions. Other suitable fragments may also be identified for such use.

15

Table I
CCV Amino Acids

	<u>B cell sites</u>	<u>T cell sites</u>	<u>SEQ ID NOS:</u>
	50-250		3
	375-425		4
20	450-470		5
	550-600		6
	650-700		7
	770-850		8
	900-1025		9
25	1150-1225		10
	1250-1452		11
		40-47	12
		63-81	13
		187-191	14
30		241-274	15
		335-341	16
		395-428	17
		468-494	18
		846-860	19
35		916-952	20
		977-992	21
		1068-1145	22
		1366-1391	23

Table II

Amino Acid Sequences

	<u>CCV 1-71</u> <u>Amino Acid</u>	<u>Nucleotides</u>	% Homology CCV 1-71 to WT FIPV WSU 1146	SEQ ID NOS. AA Nucl.
5	1113-1236	3337-3708	100	25 and 24
	540-599	1618-1797	93.3	27 and 26
	342-388	1024-1164	93.6	29 and 28
	137-153	409-459	64.7	31 and 30
10	375-388	1123-1164	85.7	33 and 32
	1424-1440	4270-4320	94.1	35 and 34
	1407-1420	4219-4260	85.7	37 and 36
	1342-1406	4024-4218	96.9	39 and 38
	398-652	1192-1956	93.3	41 and 40
15	128-555	382-1665	89.5	43 and 42
	447-628	1339-1884	91.8	45 and 44

IV. Modified Sequences of the Invention.

20 In addition to the amino acid sequences and corresponding nucleotide sequences of the specifically-recited embodiments of CCV S proteins of this invention, the invention also encompasses other DNA and amino acid sequences of CCV S proteins. Such other nucleic acid sequences include those sequences capable of hybridizing to SEQ ID NO: 1 under conditions of at least 85% stringency, i.e. having at least 85% homology to the sequence of SEQ ID NO: 1, more preferably at least 90% homology, and most preferably at least 95% homology. Such homologous sequences are characterized by encoding a CCV S gene 25 protein related to strain 1-71.

30

Further, allelic variations (naturally-occurring base changes in the species population which may or may not result in an amino acid change) of DNA sequences encoding the various S amino acid or DNA sequences from the illustrated CCV are also included in the present invention, as well as analogs or derivatives thereof. Similarly, DNA sequences which code for protein sequences of the invention but which differ in codon sequence due to the degeneracies of the genetic code or variations in the DNA sequence encoding these proteins which are caused by point mutations or by induced modifications to enhance the activity, half-life or production of the peptide encoded thereby are also encompassed in the invention.

Variations in the amino acid sequences of this invention may typically include analogs that differ by only 1 to about 4 codon changes. Other examples of analogs include polypeptides with minor amino acid variations from the natural amino acid sequence of S gene proteins and/or the fusion partner; in particular, conservative amino acid replacements. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are generally divided into four families: (1) acidic = aspartate, glutamate; (2) basic = lysine, arginine, histidine; (3) non-polar = alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar = glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar conservative replacement of an amino acid with a structurally related

amino acid will not have a significant effect on its activity, especially if the replacement does not involve an amino acid at an epitope of the polypeptides of this invention.

5 V. *Fusion Proteins.*

If desired, the CCV S proteins and peptide fragments, e.g. those identified in Tables I and II, can be produced in the form of fusion proteins as defined below. Such a fusion protein may contain either a full-length CCV S protein or an immunogenic fragment thereof. Suitable fragments include those contained within SEQ ID NO: 2 and the amino acids fragments of Tables I and II. Other suitable fragments can be determined by one of skill in the art by analogy to the sequences provided herein.

15 Proteins or peptides may be selected to form fusion proteins with the selected S protein or peptide sequence based on a number of considerations. The fusion partner may be a preferred signal sequence, a sequence which is characterized by enhanced secretion in a selected host cell system, or a sequence which enhances the stability or presentation of the S-derived peptide. Such exemplary fusion partners include, without limitation, ubiquitin and α mating factor for yeast expression systems, and beta-galactosidase and influenza NS-1 protein for bacterial systems. One of skill in the art can readily select an appropriate fusion partner for a selected expression system. The present invention is not limited to the use of any particular fusion partner.

20 The CCV S protein or fragments thereof can optionally be fused to each other or to the fusion partner through a conventional linker sequence, i.e., containing about 2 to 50 amino acids, and more preferably, about 2 to about 20 amino acids in length. This optional linker may provide space between the two linked sequences.

Alternatively, this linker sequence may encode, if desired, a polypeptide which is selectively cleavable or digestible by conventional chemical or enzymatic methods. For example, the selected cleavage site may be an enzymatic cleavage site, including sites for cleavage by a proteolytic enzyme, such as enterokinase, factor Xa, trypsin, collagenase and thrombin. Alternatively, the cleavage site in the linker may be a site capable of being cleaved upon exposure to a selected chemical, e.g., cyanogen bromide or hydroxylamine. The cleavage site, if inserted into a linker useful in the fused sequences of this invention, does not limit this invention. Any desired cleavage site, of which many are known in the art, may be used for this purpose.

15 VI. *Production of Sequences of Invention*

The CCV S gene protein of the invention and amino acid regions, fragments thereof and their corresponding nucleotide sequences, as well as other proteins described herein, e.g. fusion partners, may be produced by conventional methods. These proteins or fragments and the nucleotide sequences may be prepared by chemical synthesis techniques [Merrifield, J.A.C.S., 85:2149-2154 (1963)]. Preferably, however, they are prepared by known recombinant DNA techniques by cloning and expressing within a host microorganism or cell a DNA fragment carrying a coding sequence for the selected protein. See, e.g., Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2nd edit., Cold Spring Harbor Laboratory, New York (1989). Such techniques are discussed below in the Examples.

30 According to cloning techniques, a selected gene fragment of this invention can be cloned into a selected expression vector. Vectors for use in the method of producing S protein proteins comprise a novel S gene DNA sequence (or a fragment thereof) of the invention and

selected regulatory sequences in operative association with the DNA coding sequence, and capable of directing the replication and expression of the peptide in a selected host cell.

5 Vectors, e.g., polynucleotide molecules, of the invention may be designed for expression of CCV S proteins and/or fusion proteins in bacterial, mammalian, fungal or insect cells or in selected viruses. Suitable vectors are known to one skilled in the art by resort to known 10 publications or suppliers.

15 The resulting DNA molecules or vectors containing nucleotide sequences encoding the canine coronavirus S peptides or fragments thereof and/or encoding the fusion proteins are then introduced into host cells and expression of the heterologous protein induced.

20 Additional expression systems may include the known viral expression systems, e.g., vaccinia, fowlpox, swine pox. It is understood additionally, that the design of the expression vector will depend on the choice of host cell. A variety of suitable expression systems in any of the below-identified host cells are known to those skilled 25 in the art and may be readily selected without undue effort.

25 Suitable cells or cell lines for use in expressing the S protein or peptides of this invention can be eukaryotic or prokaryotic. A preferred expression system includes mammalian cells, such as Chinese Hamster ovary cells (CHO) or COS-1 cells. The selection of other suitable mammalian host cells and methods for transformation, culture, amplification, screening and 30 product production and purification are known in the art. See, e.g., Gething and Sambrook, Nature, 293:620-625 (1981), or alternatively, Kaufman et al, Mol. Cell. Biol.,

5 (7):1750-1759 (1985) or Howley et al, U. S. Patent 4,419,446. Also desirable are insect cell systems, such as the baculovirus or *Drosophila* systems. The selection of other suitable host cells and methods for transformation, culture, amplification, screening and product production and purification can be performed by one of skill in the art by reference to known techniques. See, e.g., Gething and Sambrook, *Nature*, 293:620-625 (1981).

10 After the transformed host cells are conventionally cultured for suitable times and under suitable culture conditions known to those skilled in the art, the cells may be lysed. It may also be possible, depending on the construct employed, that the recombinant proteins are secreted extracellularly and obtained from the culture medium. Cell lysates or culture medium are then screened for the presence of CCV S protein or peptide which are recognized by antibodies, preferably monoclonal antibodies (MAbs), to a peptide antigenic site from CCV.

20 Similarly, the fusion proteins may be produced by resort to chemical synthesis techniques, or preferably, recombinant methods, as described above. The selected primer sets used in the PCR reaction described in the Examples below may be designed to produce PCR amplified fragments containing restriction endonuclease cleavage site sequences for introduction of a canine coronavirus S gene fragment in a specific orientation into a selected expression vector to produce fusion proteins of the invention. The vector may contain a desired protein or fragment thereof to which the S gene fragment is fused in frame to produce a fusion protein.

25 30 The crude cell lysates containing the CCV S protein or peptides or fusion proteins can be used directly as vaccinal components, therapeutic compositions or

diagnostic reagents. Alternatively, the CCV S peptides can be purified from the crude lysate or medium by conventional means.

VII. Vaccine Compositions

5 The CCV S proteins and immunogenic fragments of this invention may be incorporated in a vaccine composition. Such a vaccine composition may contain an immunogenic amount of one or more selected CCV S peptides or proteins, e.g., encoded by the complete S gene sequence 10 of CCV or partial sequences thereof, and prepared according to the method of the present invention, together with a carrier suitable for administration as a vaccine composition for prophylactic treatment of CCV infections. The protein may be in the form of a fusion protein as 15 above-described. Alternatively, the CCV S gene or fragment may be incorporated into a live vector, e.g., adenovirus, vaccinia virus and the like. The expression of vaccinal proteins in such live vectors are well-known to those in the art [See, e.g., U. S. Patent No. 4,920,209]. It is 20 preferable that the protein employed in the vaccine composition induces protective immune responses against more than one strain of CCV.

25 A vaccine composition according to the invention may optionally contain other immunogenic components. Particularly desirable are vaccine compositions containing other canine antigens, e.g., canine distemper, *Borrelia burgdorferi*, canine *Bordetella*, rabies, canine parvovirus, *Leptosporidia* sp., canine rotavirus, canine parainfluenza virus and canine adenovirus.

30 In another embodiment, the CCV S proteins may be used in a combination vaccine directed to related coronaviruses. Other suitable coronaviruses which can be used in such a combination vaccine include a feline coronavirus, such as FIPV or FECV. For example, a CCV S 35 peptide or protein of the present invention may be employed

as an additional antigen in the temperature sensitive FIPV vaccine described in detail in co-owned, co-pending U. S. Patent Application Ser. No. 07/428,796 filed October 30, 1989, incorporated by reference herein. Alternatively, the 5 CCV S protein or peptide or a fragment thereof could be used in a vaccine composition containing other coronavirus S proteins or fragments thereof, particularly those described in co-pending, co-owned U.S. Patent application Ser. No. 07/698,927 (and its corresponding published PCT 10 Application No. WO92/08487).

The preparation of a pharmaceutically acceptable vaccine composition, having appropriate pH isotonicity, stability and other conventional characteristics is within the skill of the art. Thus such vaccines may optimally 15 contain other conventional components, such as adjuvants and/or carriers, e.g. aqueous suspensions of aluminum and magnesium hydroxides, liposomes and the like.

The vaccine composition may be employed to 20 vaccinate animals against the clinical symptoms associated with CCV. The vaccines according to the present invention can be administered by an appropriate route, e.g., by the oral, intranasal, subcutaneous, intraperitoneal or intramuscular routes. The presently preferred methods of administration are the subcutaneous and intranasal routes.

25 The amount of the CCV S peptide or protein of the invention present in each vaccine dose is selected with regard to consideration of the animal's age, weight, sex, general physical condition and the like. The amount required to induce an immunoprotective response in the 30 animal without significant adverse side effects may vary depending upon the recombinant protein employed as immunogen and the optional presence of an adjuvant.

Generally, it is expected that each dose will comprise between about 0.05-5000 micrograms of protein per mL, and preferably 0.05-100 micrograms per mL of a sterile solution of an immunogenic amount of a protein or peptide of this invention. Initial doses may be optionally followed by repeated boosts, where desirable.

Another vaccine agent of the present invention is an anti-sense RNA sequence generated to the S gene of CCV strain 1-71 [SEQ ID NO:1] [S. T. Crooke et al, Biotech., 10:882-886 (Aug. 1992)]. This sequence may easily be generated by one of skill in the art either synthetically or recombinantly. Under appropriate delivery, such an anti-sense RNA sequence when administered to an infected animal should be capable of binding to the RNA of the virus, thereby preventing viral replication in the cell.

VIII. *Pharmaceutical Compositions*

The invention also provides a pharmaceutical composition comprising one or more CCV S peptides or proteins prepared according to the present invention and a pharmaceutically effective carrier. Suitable pharmaceutically effective carriers for internal administration are known to those skilled in the art. One selected carrier is sterile saline. The pharmaceutical composition can be adapted for administration by any appropriate route, but is designed preferentially for administration by injection or intranasal administration.

IX. *Antibodies of the Invention*

The present invention also encompasses the development of an antibody to one or more epitopes in the above identified amino acid sequences derived from the CCV S protein, which epitope is distinct from those of other CCV strains or other coronaviruses, e.g. FIPV, TGEV or FECV. The antibody can be developed employing as an antigenic substance, a peptide of Table I or II.

Alternatively, other regions of the CCV strain 1-71 S protein SEQ ID NO: 2 may be employed in the development of an antibody according to conventional techniques.

5 In one embodiment, the antibody is capable of identifying or binding to a CCV antigenic site encoded by SEQ ID NO: 1 or a fragment thereof. Such an antibody may be used in a diagnostic screening test, e.g., as a hybridization probe, or as a therapeutic agent.

10 Antibodies which bind CCV peptides from the regions identified above or to other regions capable of distinguishing between CCV, TGEV, FIPV, FECV, and other coronaviruses for use in the assays of this invention may be polyclonal. However, it is desirable for purposes of increased target specificity to utilize MAbs, both in the 15 assays of this invention and as potential therapeutic and prophylactic agents. Additionally, synthetically designed MAbs may be made by known genetic engineering techniques [W. D. Huse et al, Science, 246:1275-1281 (1989)] and employed in the methods described herein. For purposes of 20 simplicity the term MAb(s) will be used throughout this specification; however, it should be understood that certain polyclonal antibodies, particularly high titer polyclonal antibodies and recombinant antibodies, may also be employed.

25 A MAb may be generated by the well-known Kohler and Milstein techniques and modifications thereof and directed to one or more of the amino acid residue regions identified above, or to other CCV S peptides or epitopes containing differences between CCV strain 1-71 and other 30 coronaviruses. For example, a fragment of SEQ ID NO: 2 which represents an antigenic site, which differs from that of FIPV, may be presented as an antigen in conventional

techniques for developing MAbs. One of skill in the art may generate any number of MAbs by using fragments of the amino acid residue regions identified herein as an immunogen and employing these teachings.

5 For diagnostic purposes, the antibodies (as well as the diagnostic probes) may be associated with individual labels. Where more than one antibody is employed in a diagnostic method, the labels are desirably interactive to produce a detectable signal. Most desirably, the label is detectable visually, e.g. colorimetrically. Detectable labels for attachment to antibodies useful in the diagnostic assays of this invention may also be easily selected by one skilled in the art of diagnostic assays, among which include, without limitation, horseradish 10 peroxidase (HRP) or alkaline phosphatase (AP), hexokinase in conjunction with glucose-6-phosphate dehydrogenase, and NAD oxidoreductase with luciferase and substrates NADH and 15 FMN or peroxidase with luminol and substrate peroxide. These and other appropriate label systems and methods for 20 coupling them to antibodies or peptides are known to those of skill in the art.

Antibodies may also be used therapeutically as targeting agents to deliver virus-toxic or infected cell-toxic agents to infected cells. Rather than being 25 associated with labels for diagnostic uses, a therapeutic agent employs the antibody linked to an agent or ligand capable of disabling the replicating mechanism of the virus or of destroying the virally-infected cell. The identity of the toxic ligand does not limit the present invention. 30 It is expected that preferred antibodies to peptides encoded by the S genes identified herein may be screened for the ability to internalize into the infected cell and deliver the ligand into the cell.

X. *Diagnostic Reagents and Assays*

The nucleotide sequences, amino acid fragments and antibodies described above may be employed as diagnostic reagents for use in a variety of diagnostic methods according to this invention.

5 A. PCR Diagnostic Assays.

For example, these sequences can be utilized in a diagnostic method employing the polymerase chain reaction (PCR) technique to identify the presence of a CCV or CCV-like virus and in therapy of infected animals.

10 In addition to those sequences identified above, the oligonucleotide sequences that were designed to prime cDNA synthesis at specific sites within the CCV S gene, as described in detail below in Example 3 [SEQ ID NO:46-50], may also be employed as diagnostic reagents according to this invention. These sequences, as well as the below-described optimized conditions for the PCR amplification of CCV fragments therefrom, may also be employed in a diagnostic method.

15 The PCR technique is known to those of skill in the art of genetic engineering and is described in detail in Example 4 [see, e.g., R. K. Saiki et al, Science, 230:1350-1354 (1985)], which is incorporated herein by reference. Briefly described, PCR employs two 20 oligonucleotide primers which are complementary to the opposite strands of a double stranded nucleic acid of interest whose strands are oriented such that when they are extended by DNA polymerase, synthesis occurs across the region which separates the oligonucleotides. By repeated 25 cycles of heat denaturation, annealing of the primers to their complementary sequences and extension of the annealed primers with a temperature stable DNA polymerase, millions 30 of copies of the target gene sequence are generated. The template for the reaction is total RNA, which is isolated

from CCV infected cells. DNA fragments generated by PCR were amplified from cDNA which had been synthesized from this RNA. Other strains of CCV or CCV-related sequences may also provide PCR templates in a similar manner.

5 In one diagnostic method, for example, heterogenous CCV gene sequences of this invention are useful as reagents in diagnostic assays to detect and distinguish the presence of specific viruses from each other, e.g., to distinguish one canine coronavirus strain from another or one species of coronavirus from another by means of conventional assay formats. For example, using 10 protocols similar to those used for forensic purposes, tissue or blood samples from a dog suspected to be infected with CCV would be subjected to PCR amplification with a selected CCV-specific set of primers, such as those DNA 15 sequences disclosed herein. Amplification of DNA from a sample tissue or biological fluid of the animal suspected of infection using nucleotide sequences as primers specific for regions of the CCV viral gene sequences could correlate 20 to the presence of CCV. Absence of CCV in the sample would result in no amplification. Similarly, the selection of specific sets of S gene primers would allow the 25 identification of a particular strain of CCV as well. Thus, appropriate treatments may be selected for the infected animal.

Example 3 provides oligonucleotide primers which permitted the synthesis of regions of the CCV S gene. The nucleotide sequence of the S gene of CCV provides desirable sequences for hybridization probes and PCR primers, for example, the sequences between nucleotide base pairs 900 to 30 about 1600 [SEQ ID NO: 55] and about 2500 to about 3900 [SEQ ID NO: 56] of SEQ ID NO: 1. Smaller or larger DNA fragments in these regions may also be employed as PCR primers or hybridization probes.

It is desirable to have PCR primer sequences between 15 to 30 bases in length, with an intervening sequence of at least 100 bases to as large as 5000 bases there between, according to conventional PCR technology. 5 However, it is possible that larger or smaller sequence lengths may be useful based upon modifications to the PCR technology. In general, in order to achieve satisfactory discrimination, a hybridization or oligonucleotide probe made up of one or more of these sequences would consist of 10 between 15 and 50 bases in length based on current technology.

B. Conventional Assay Formats

The CCV S proteins or peptide fragments may also be employed in standard diagnostic assays which rely on S protein immunogens as targets for sera recognition. The diagnostic assays may be any conventionally employed assay, e.g., a sandwich ELISA assay, a Western blot, a Southern blot and the like. Because a wide variety of diagnostic methods exist and are conventionally known which can be adapted to the use of the nucleotide and amino acid sequences described herein, it should be understood that the nature of the diagnostic assay does not limit the use of the sequences of this invention.

For example, the amino acid sequences encoded by 25 CCV S gene sequences, such as those appearing in Tables I and II above, which may be amplified by PCR, provide peptides useful in such diagnostic assays as ELISA or Western assay, or as antigens for the screening of sera or development of antibodies.

For example, the sequences between about amino acid 1 to about 250 [SEQ ID NO:57], about 450 to about 650 [SEQ ID NO:58], and about 900 to about 1150 [SEQ ID NO:59] of the CCV strain 1-71 S gene protein SEQ ID NO:2, are anticipated to be useful as such antigens. Such peptides 30 can optionally also be used in the design of synthetic

peptide coupled to a carrier for diagnostic uses, e.g., antibody detection in sera. Suitable carriers include ovalbumin, keyhole limpet hemocyanin, bovine serum albumin, sepharose beads and polydextran beads.

5 Such peptide antigens and antibodies to these peptides would react positively with tissue or serum samples of dogs infected with CCV, but negatively with non-CCV infected dogs. These antibodies are discussed in more detail below.

10 For example, the invention provides a method of using the full length CCV S protein or fragments thereof as diagnostic agents for identifying the presence or absence of antibodies in previously exposed, naive or vaccinated dogs, respectively, as well as for differentiating exposure to CCV from other related coronaviruses. Other S peptides or fusion proteins which show differential reactivity to CCV and other coronavirus sera may also be useful as CCV-specific reagents in ELISA-based screening assays to detect CCV exposure in dogs. Similarly, an S protein or peptide 15 which contains epitopes recognized only by sera from CCV infected dogs or by sera from CCV positive dogs could be employed to distinguish or differentiate among coronavirus 20 infections.

25 As one assay format, the reactivity of affinity purified CCV S proteins or peptides fragments to canine biological fluids or cells can be assayed by Western blot. The assay is preferably employed on sera, but may also be adapted to be performed on other appropriate fluids or cells, for example, macrophages or white blood cells. In 30 the Western blot technique, the purified protein, separated by a preparative SDS polyacrylamide gel, is transferred to

nitrocellulose and cut into multiple strips. The strips are then probed with dog sera from uninfected or infected dogs. Binding of the dog sera to the protein is detected by incubation with alkaline phosphatase tagged goat anti-dog IgG followed by the enzyme substrate BCIP/NBT. Color development is stopped by washing the strip in water.

CCV S protein or fragments thereof may also be used in an ELISA based assay for detecting CCV disease. A typical ELISA protocol would involve the adherence of antigen (e.g., a S protein) to the well of a 96-well tray. The serum to be tested is then added. If the serum contains antibody to the antigen, it will bind. Specificity of the reaction is determined by the antigen absorbed to the plate. With the S protein, only sera from those dogs infected with CCV would bind to the plate; sera from naive or uninfected dogs would not bind.

Similarly, a CCV S protein or peptide which contained epitopes recognized only by sera from CCV-infected dogs or by sera from CCV-positive dogs could be employed to distinguish coronavirus infections. After the primary antibody is bound, an enzyme-labeled antibody directed against the globulin of the animal whose serum is tested is added. Substrate is then added. The enzyme linked to antibody bound to the well will convert the substrate to a visible form. The amount of color measured is proportional to the amount of antibody in the test material. In this manner, dogs infected with CCV can be identified and treated, or dogs naive to the virus can be protected by vaccination.

When used as diagnostic reagents, the primers, probes, peptide antigens, nucleotide sequence encoding or flanking a CCV S protein or fragment of the invention, and antibodies of this invention may be optionally associated with detectable labels or label systems known to those

skilled in the art. Such labelled diagnostic reagents may be used to assay for the presence of CCV in dogs in hybridization assays or in the PCR technique as described above.

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C. Diagnostic Kits

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The assay methods, PCR primers, CCV S nucleotide sequences [SEQ ID NO:1], S proteins and peptides, and antibodies described herein may be efficiently utilized in the assembly of a diagnostic kit, which may be used by veterinarians or laboratories. The kit is useful in distinguishing between CCV infected animals and vaccinated animals, as well as non-exposed dogs, and between CCV-infected animals and animals infected with serologically related viruses, such as other CCV or FIPV, TGEV, and FECV. Such a diagnostic kit contains the components necessary to practice the assays described above.

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Thus, the kit may contain a sufficient amount of at least one CCV S protein, fusion protein or peptide fragment, at least one CCV S gene nucleotide sequence or PCR primer pair of this invention, a MAb directed to a first epitope on the CCV S protein (which MAb may be labeled), optional additional components of a detectable labelling system, vials for containing the serum samples, protein samples and the like, and a second MAb conjugated to the second enzyme, which in proximity to the first enzyme, produces a visible product. Other conventional components of such diagnostic kits may also be included.

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Alternatively, a kit may contain a selected CCV S protein or peptide, a MAb directed against a selected CCV S peptide fragment bound to a solid surface and associated with a first enzyme, a different MAb associated with a second enzyme, and a sufficient amount of the substrate for the first enzyme, which, when added to the serum and MAbs, provides the reactant for the second enzyme, resulting in the color change.

Other known assay formats will indicate the inclusion of additional components for a diagnostic kit according to this invention.

5 The following examples illustrate the embodiments of this invention and do not limit the scope of the present invention.

Example 1 - Isolation of ccv

10 Canine coronavirus strain 1-71 was isolated in 1971 from military dogs suffering from a viral gastroenteritis by Binn et al., Proceeding 78th Annual Meeting U.S. Animal Health Association, October 1974, p. 359-366. The initial isolate from the feces of the 15 infected dog was grown in tissue culture on the PrDKTCA72 dog cell line [ATCC No. CRL 1542]. The coronavirus strain used in this study was received from the ATCC (ATCC #VR-809, ccv Strain 1-71, Frozen lot#4, Passage 7/PDK, 17 May 1988) and passaged five times on PrDKTCA72.

Example 2 - RNA purification

20 After the fifth passage the infected cells were processed for RNA isolation by infecting a 1700 cc² roller bottle with a CCV inoculum. The inoculum was prepared by diluting 2.5 μ l of infected fluids from a confluent monolayer into 13.0 mls of media. One ml of this material 25 was used to infect a roller bottle and the cells were grown until they demonstrated a pronounced cytopathic effect at 48 hours. The infected monolayers were harvested and total cytoplasmic RNA was extracted using the guanidinium thiocyanate procedure as described in Chirgwin et al., Biochem., 18:5294 (1979).

Example 3 - Primers Used for PCR Amplification of ccv Spike Gene Fragments

The primers appearing below in Table III were synthesized conventionally by the phosphoramidite method and gel purified prior to use. Primer #3045 was based on an FECV S gene sequence; and primers #4920, 1923, 2443 and 2600 were based on WT FIPV WSU 1146 sequences.

Table III

	Amplified S Gene Region	Cloned Region	Top Primer	Bottom Primer
	1-362 aa	1-352 aa	# 3045	# 4920
15	352-1452 aa	352-1452 aa	# 2600	# 1923
	1-555 aa	128-555 aa	# 3045	# 2443
	<u>Primer #</u> <u>DNA Sequence</u>			
	1923 [SEQ ID NO:46]	TAAAT <u>AGGCCT</u> TTAGTGGACATGCAC StuI		
20	2443 [SEQ ID NO:47]	TTAGT <u>AGGCCT</u> GTCGAGGCTATGGGTTGACCATAACCAC StuI		
	2600 [SEQ ID NO:48]	CAGAT <u>CCCGGGT</u> TACAATCTGGTATGGGTGCTACAG XmaI		
25	3045 [SEQ ID NO:49]	GTGCC <u>CCCGGGT</u> ATGATTGTGCTCGTAAC <u>TGCCT</u> TTG XmaI		
	4920 [SEQ ID NO:50]	AGCACCCATACCAGATTGTACAT <u>CTGCAGT</u> GAAATTAGATTG PstI		

Example 4 - PCR Amplification of CCV S Gene

30 PCR amplified fragments of CCV S gene were generated using the following procedure. All PCR reagents were supplied by Perkin Elmer-Cetus, Norwalk, CT. In a final reaction volume of 20 μ l of 1X RT buffer (5X RT buffer: 250 mM Tris-HCl, pH 8.3, 375 mM KCl, 15 mM MgCl₂),

the following components were assembled in RNase-free siliconized 500 μ l microcentrifuge tubes: 1.0 mM of each dNTP, 20 units of RNasin [Promega Corp, Madison, WI], 2.5 picomoles of random hexamer oligonucleotides [Pharmacia, Milwaukee, WI], 100 picomoles/ μ l solution in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.5), 200 units of reverse transcriptase [Superscript RT, Bethesda Research Labs, Gaithersburg, MD] and 1.0 μ g of respective RNA isolated as described above in Example 3. To avoid pipetting errors and contamination, all solutions were aliquoted from master mixes made with diethyl pyrocarbonate (DEPC) treated water and consisted of all of the reaction components except the RNA which was added last.

The mixture was incubated in a programmable thermal cycler [Perkin-Elmer Cetus, Norwalk, CT] at 21°C for ten minutes followed by 42°C for one hour then 95°C for five minutes and finally held at 4°C until PCR amplification.

Amplification of the cDNA was performed essentially according to the method of R. K. Saiki et al, Science, 230:1350-1354 (1985) using the Taq polymerase. Briefly, to the 20 μ l cDNA reaction mix from above was added 10.0 μ l 10X PCR buffer, 1.0 μ l of each upstream and downstream primer previously diluted in water to 30 picomoles per microliter and 2.5 units of Taq polymerase (Perkin-Elmer Cetus, Norwalk, CT). Final volume was made up to 100 μ l using DEPC treated water and overlaid with 100 μ l of mineral oil. As above, master mixes were prepared to avoid contamination. The reaction was performed in the Perkin-Elmer Cetus thermal cycler for one cycle by denaturing at 95°C for 1 minute, annealing at 37°C for 3 minutes followed by an extension at 72°C for 40 minutes.

This initial cycle increased the likelihood of first strand DNA synthesis. A standard PCR profile was then performed by a 95°C for 1 minute denaturation, 37°C for 3 minutes annealing, 72°C for 3 minutes extension for 40 cycles. A 5 final extension cycle was done by 95°C for 1 minute denaturation, 37°C for 2 minutes annealing, 72°C for 15 minutes extension and held at 4°C until analyzed.

PCR products were analyzed by electrophoresing 5.0 μ l of the reaction on a 1.2% agarose gel for 16-17 10 hours. Bands were visualized by ethidium bromide staining the gel and fluorescence by UV irradiation at 256 nm. Photography using Polaroid type 55 film provided a negative that could be digitized for sample distance migration and 15 comparison against markers run on each gel. The actual sizes of the bands were then calculated using the Beckman Microgenie software running on an IBM AT.

Example 5 - Cloning of CCV Spike Gene Regions

Cloning procedures were performed substantially as described by Maniatis et al, cited above. Details of 20 the clonings are provided in the following examples. Calf-alkaline phosphatase was from Bethesda Research Labs (Gaithersburg, MD). Ligation products were transformed into *E. coli* host strain XL1 Blue [Stratagene Cloning Systems, La Jolla, CA]. pBluescript SK_BM13-phagemid vector 25 was also obtained from Stratagene Cloning Systems. All restriction enzymes were purchased from New England Biolabs (Beverly, MA) or Bethesda Research Labs (Gaithersburg, MD) and used according to manufacturer's specifications. T4 DNA ligase was received from Boehringer Mannheim Biochemicals (Indianapolis, IN). Calf intestinal alkaline phosphatase was purchased from Bethesda Research Labs. 30

Example 6 - CCV S Protein Fragment, A.A. 1-128 [SEQ ID NO:511]

Five microliters (approximately 200 ng) of PCR-amplified DNA representing amino acids 1-362 [SEQ ID NO:53] of the CCV spike gene were ligated to the pT7Blue T-Vector (Novagen, Madison, WI) as per the manufacturer's instructions. One microliter of the ligation mix was used to transform NovaBlue competent cells (Novagen) and transformation mixes were plated on LB plates supplemented with ampicillin, isopropylthio- β -galactoside (IPTG; Sigma Chemical Co., St. Louis, MO), and 5-bromo-4-chloro-3-indolyl- β -D-galactoside (X-gal; Sigma Chemical Co., St. Louis, MO). White colonies were picked and screened by restriction analysis of mini-prep DNA. Insert-bearing clones were identified and oriented with respect to vector by SmaI/PstI, StuI, and PstI digests. Clone #2964 contained a full-length 1-362 amino acid insert and was used to provide sequence analysis from 1-128 amino acids of the CCV S gene.

Example 7 - CCV S Protein Fragment, A.A. 128-555 [SEQ ID NO:431]

10 μ l of PCR DNA encoding 1-555aa of the CCV spike protein was digested with SmaI/StuI for 4 hours at room temperature. DNA bands were isolated and purified from low-melting temperature agarose gels as described by Maniatis et al, cited above. Briefly, DNA fragments were visualized after staining with ethidium bromide, excised from the gel with a scalpel and transferred to microfuge tubes. Gel slices were incubated 5 min at 65°C, vortexed, and 5 volumes of 20 mM Tris, pH 8.0, 1 mM EDTA were added.

Samples were incubated an additional 2 minutes at 65°C and were then extracted once with phenol and again with phenol:chloroform. The DNA was precipitated with 1/10 volume 3 M NaOAc, pH 7.0, and 2.5 volumes of cold 95% ETOH overnight at -20°C. Insert DNAs were ligated to SK_RM13-SmaI-digested, dephosphorylated vector [Stratagene] for 4 hours at room temperature. Insert-bearing clones were identified by XhoI/SstI and BglI digests of mini-prep DNA. Restriction enzyme and sequence analysis indicated that the cloned insert was short by ~300bp due to the presence of a StuI site at amino acid #128 of the CCV spike gene. Therefore, these clones contained the CCV S protein spanning amino acids from about 128-555 [SEQ ID NO:43].

Example 8 - CCV S Protein Fragment, A.A. 352-1452 [SEQ ID NO:52]

PCR-amplified DNA fragments encoding amino acids 352-1454 of the CCV spike protein were purified using Prime-Erase Quik Columns [Stratagene] according to the manufacturer's instructions. Column-purified DNAs were then digested with XmaI/EcoRV overnight at 15°C and subsequently isolated and eluted from low-melting temperature agarose gels as described by Maniatis et al, cited above. Inserts were ligated overnight at 15°C to SK_RM13- XmaI/StuI digested, dephosphorylated vector [Stratagene]. Clones were identified and oriented with respect to vector by XhoI/SstI and PvuII digests of mini-prep DNAs, respectively.

Example 9 - DNA Sequencing

DNA sequence for the CCV S gene was determined from the individual clones #1775 (AA 352-1452; SEQ ID NO:52), #2007 (AA 128-555; SEQ ID NO:43) and #2964 (AA 1-362; SEQ ID NO:53). Nested set deletions were prepared from each clone or internal primers synthesized to

facilitate primer walking and the sequence determined from both strands [Lark Sequencing Technologies, Houston, TX]. The chain termination method performed as described in Sanger et al, Proc. Natl. Acad. Sci. USA, 74:5463-5467 5 (1977) was used to determine the sequence of all clones. The full length sequence of the CCV S gene was assembled from overlapping sequences of each of the three separate fragments by computer analysis.

DNA sequence analysis was performed using either 10 Beckman Microgenie programs on an IBM Model PS/2 Model 70 or the University of Wisconsin GCG package of programs implemented on a DEC VAX cluster [Devereau et al., (1984)].

SEQ ID NO:1 is the complete nucleotide sequence of the CCV strain 1-71 S gene. The amino acid [SEQ ID NO:2] and nucleotide sequences [SEQ ID NO:1] of CCV 1-71 total 1452 amino acids and 4356 base pairs. CCV 1-71 has a DNA homology of 90.8% to published FIPV strain WT WSU 1146, 93.2% identity with FIPV strain DF2 and 94.1% similarity with FECV. In comparison to WSU 1146, this CCV 20 strain further contains two amino acid deletions at positions 11 and 12, and two amino acid insertions at positions 118 and 119. In comparison to the amino acid sequences of other coronavirus S genes, the amino acid sequence of CCV is 82.2% homologous to TGEV, 89.7% 25 homologous to DF2-HP, 90.0% homologous to TS-BP, 92.9% homologous to TS, 93.2% homologous to DF2, and 94.1% homologous to FECV.

The canine coronavirus S gene encoding amino acids #225-1325 [SEQ ID NO:54] has an overall homology to the published WT FIPV WSU 1146 strain at amino acids 352 to 1454 of 95.9%. The homology level is increased to 97.5% when the comparison is done under the amino acid similarity rules as proposed by M. O. Dayhoff, *Atlas of Protein*

Sequence and Structure, Vol. 5, Supp. 3, Natl. Biomed. Res. Found., Washington, DC (1978). There are 42 amino acid differences between the CCV S gene and the published sequence of WSU 1146 strain within the CCV sequence of SEQ ID NO: 2. Other CCV fragment homologies with WT FIPV WSU 1146 are illustrated in Table II above.

Numerous modifications and variations of the present invention are included in the above-identified specification and are expected to be obvious to one of skill in the art. Such modifications and alterations to the compositions and processes of the present invention are believed to be encompassed in the scope of the claims appended hereto.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Miller, Timothy J.
Klepfer, Sharon
Reed, Albert Paul
Jones, Elaine V.

(ii) TITLE OF INVENTION: Canine Coronavirus S Gene and Uses
Therefor

(iii) NUMBER OF SEQUENCES: 59

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: SmithKline Beecham Corporation - Corporate
Patents
(B) STREET: 709 Swedeland Road
(C) CITY: King of Prussia
(D) STATE: PA
(E) COUNTRY: USA
(F) ZIP: 19406-2799

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US
(B) FILING DATE:
(C) CLASSIFICATION:

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(viii) PRIOR APPLICATION DATA:

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(x) ATTORNEY/AGENT INFORMATION:

(A) NAME: Schreck, Patricia A.
(B) REGISTRATION NUMBER: 33,777
(C) REFERENCE/DOCKET NUMBER: SBC H85010-1

(xi) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (215) 270-5015
(B) TELEFAX: (215) 270-5090

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4359 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..4356

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATG ATT GTG CTC GTA ACT TGC CTC TTG TTT TCG TAC AAT AGT GTG ATT	48
Met Ile Val Leu Val Thr Cys Leu Leu Phe Ser Tyr Asn Ser Val Ile	
1 5 10 15	
TGT ACA TCA AAC AAT GAC TGT GTA CAA GTT AAT GTG ACA CAA TTG CCT	96
Cys Thr Ser Asn Asn Asp Cys Val Gln Val Asn Val Thr Gln Leu Pro	
20 25 30	
GGC AAT GAA AAC ATT ATT AAA GAT TTT CTA TTT CAC ACC TTC AAA GAA	144
Gly Asn Glu Asn Ile Ile Lys Asp Phe Leu Phe His Thr Phe Lys Glu	
35 40 45	
GAA GGA AGT GTA GTT GGT GGT TAT TAC CCT ACA GAG GTG TGG TAT	192
Glu Gly Ser Val Val Gly Gly Tyr Tyr Pro Thr Glu Val Trp Tyr	
50 55 60	
AAC TGC TCC AGA AGC GCA ACA ACC ACC GCT TAC AAG GAT TTT AGT AAT	240
Asn Cys Ser Arg Ser Ala Thr Thr Ala Tyr Lys Asp Phe Ser Asn	
65 70 75 80	
ATA CAT GCA TTC TAT TTT GAT ATG GAA GCC ATG GAG AAT AGT ACT GGC	288
Ile His Ala Phe Tyr Phe Asp Met Glu Ala Met Glu Asn Ser Thr Gly	
85 90 95	
AAT GCA CGA GGT AAA CCT TTA CTA GTA CAT GTT CAT GGT GAT CCT GTT	336
Asn Ala Arg Gly Lys Pro Leu Leu Val His Val His Gly Asp Pro Val	
100 105 110	
AGT ATC ATC ATA TAT ATA TCG GCT TAT AGA GAT GAT GTG CAA GGA AGG	384
Ser Ile Ile Tyr Ile Ser Ala Tyr Arg Asp Asp Val Gln Gly Arg	
115 120 125	
CCT CTT TTA AAA CAT GGT TTG TTG TGT ATA ACT AAA AAT AAA ATC ATT	432
Pro Leu Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile Ile	
130 135 140	
GAC TAT AAC ACG TTT ACC AGC GCA CAG TGG AGT GCC ATA TGT TTG GGT	480
Asp Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu Gly	
145 150 155 160	
GAT GAC AGA AAA ATA CCA TTC TCT GTC ATA CCC ACA GGT AAT GGT ACA	528
Asp Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Gly Asn Gly Thr	
165 170 175	
AAA ATA TTT GGT CTT GAG TGG AAT GAT GAC TAT GTT ACA GCC TAT ATT	576
Lys Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr Ile	
180 185 190	
AGT GAT CGT TCT CAC CAT TTG AAC ATC AAT AAT AAT TGG TTT AAC AAT	624
Ser Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn Asn	
195 200 205	
GTG ACA ATC CTA TAC TCT CGA TCA AGC ACT GCT ACG TGG CAG AAG AGT	672
Val Thr Ile Leu Tyr Ser Arg Ser Ser Thr Ala Thr Trp Gln Lys Ser	
210 215 220	

35

GCT GCA TAT GTT TAT CAA GGT GTT TCA AAT TTT ACT TAT TAC AAG TTA Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys Leu 225 230 235 240	720
AAT AAC ACC AAT GGC TTG AAA AGC TAT GAA TTG TGT GAA GAT TAT GAA Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr Glu 245 250 255	768
TGC TGC ACT GGC TAT GCT ACC AAC GTA TTT GCC CCG ACA GTG GGC GGT Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly Gly 260 265 270	816
TAT ATA CCT GAT GGC TTC AGT TTT AAC AAT TGG TTT ATG CTT ACA AAC Tyr Ile Pro Asp Gly Phe Ser Phe Asn Asn Trp Phe Met Leu Thr Asn 275 280 285	864
AGT TCC ACG TTT GTT AGT GGC AGA TTT GTA ACA AAT CAA CCA TTA TTG Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu Leu 290 295 300	912
GTT AAT TGT TTG TGG CCA GTG CCC AGT CTT GGT GTC GCA GCA CAA GAA Val Asn Cys Leu Trp Pro Val Pro Ser Leu Gly Val Ala Ala Gln Glu 305 310 315 320	960
TTT TGT TTT GAA GGT GCG CAG TTT AGC CAA TGT AAT GGT GTG TCT TTA Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser Leu 325 330 335	1008
AAC AAT ACA GTG GAT GTC ATT AGA TTC AAC CTT AAT TTT ACC ACA GAT Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp 340 345 350	1056
GTA CAA TCT GGT ATG GGT GCT ACA GTA TTT TCA CTG AAT ACA ACA GGT Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly 355 360 365	1104
GGT GTC ATT CTT GAG ATT TCT TGT TAT AAT GAT ACA GTG AGT GAG TCA Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser 370 375 380	1152
AGT TTC TAC AGT TAT GGT GAA ATT TCA TTC GGC GTA ACT GAT GGA CCG Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly Pro 385 390 395 400	1200
CGT TAC TGT TAC GCA CTC TAT AAT GGC ACG GCT CTT AAG TAT TTA GGA Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu Gly 405 410 415	1248
ACA TTA CCA CCT AGT GTC AAG GAA ATT GCT ATT AGT AAG TGG GGC CAT Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly His 420 425 430	1296
TTT TAT ATT AAT GGT TAC AAT TTC TTT AGC ACT TTT CCT ATT GAT TGT Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp Cys 435 440 445	1344
ATA TCT TTT AAT TTA ACC ACT GGT GAT AGT GGA GCA TTT TGG ACA ATT Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr Ile 450 455 460	1392
GCT TAC ACA TCG TAC ACT GAC GCA TTA GTA CAA GTT GAA AAC ACA GCT Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr Ala 465 470 475 480	1440

ATT AAA AAG GTG ACG TAT TGT AAC AGT CAC ATT AAT AAC ATT AAA TGT Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys Cys 485 490 495	1488
TCT CAA CTT ACT GCT AAT TTG CAA AAT GGA TTT TAT CCT GTT GCT TCA Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala Ser 500 505 510	1536
AGT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA CCT AGT TTC Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser Phe 515 520 525	1584
TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG AAG CGT Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys Arg 530 535 540	1632
AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA AGT AAC ATC ACA CTA Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr Leu 545 550 555 560	1680
CCA ATG CAG GAT AAT AAC ACC GAT GTG TAC TGC ATT CGT TCT AAC CAA Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn Gln 565 570 575	1728
TTT TCA GTT TAC GTT CAT TCC ACT TGT AAA AGT TCT TTA TGG GAC GAT Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp Asp Asp 580 585 590	1776
GTG TTT AAT TCC GAC TGC ACA GAT GTT TTA TAT GCT ACA GCT GTT ATA Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val Ile 595 600 605	1824
AAA ACT GGT ACT TGT CCT TTC TCG TTT GAT AAA TTG AAC AAT TAC TTA Lys Thr Gly Thr Cys Pro Phe Ser Asp Lys Leu Asn Asn Tyr Leu 610 615 620	1872
ACT TTT AAC AAG TTC TGT TTG TCA TTG AAT CCT GTT GGT GCC AAC TGC Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn Cys 625 630 635 640	1920
AAG TTT GAT GTT GCC GCT CGT ACA AGA ACC AAT GAG CAG GTT GTT AGA Lys Phe Asp Val Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val Arg 645 650 655	1968
AGT TTA TAT GTA ATA TAT GAA GAA GGA GAC AAC ATA GTG GGT GTG CCG Ser Leu Tyr Val Ile Tyr Glu Glu Gly Asp Asn Ile Val Gly Val Pro 660 665 670	2016
TCT GAC AAT AGT GGT CTT CAC GAC TTG TCA GTG CTA CAC TTA GAC TCC Ser Asp Asn Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp Ser 675 680 685	2064
TGT ACA GAT TAT AAT ATA TAT GGT AGA ACT GGT GTT GGT ATT ATT AGA Cys Thr Asp Tyr Asn Ile Tyr Gly Arg Thr Gly Val Gly Ile Ile Arg 690 695 700	2112
CAA ACT AAC AGT ACG CTA CTT AGT GGC TTA TAT TAC ACA TCA CTA TCA Gln Thr Asn Ser Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu Ser 705 710 715 720	2160
GGT GAC TTG TTA GGG TTT AAA AAT GTT AGT GAT GGT GTC ATC TAT TCT Gly Asp Leu Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr Ser 725 730 735	2208

GTC ACG CCA TGT GAT GTA AGC GCA CAA GCT GCT GTT ATT GAT GGC GCC Val Thr Pro Cys Asp Val Ser Ala Gln Ala Ala Val Ile Asp Gly Ala 740 745 750	2256
ATA GTT GGA GCT ATG ACT TCC ATT AAT AGT GAA ATG TTA GGT CTA ACA Ile Val Gly Ala Met Thr Ser Ile Asn Ser Glu Met Leu Gly Leu Thr 755 760 765	2304
CAT TGG ACA ACA ACA CCT AAT TTT TAT TAT TAT TCT ATA TAT AAT TAT His Trp Thr Thr Pro Asn Phe Tyr Tyr Tyr Ser Ile Tyr Asn Tyr 770 775 780	2352
ACC AAT GAA AGG ACT CGT GGC ACA GCA ATT GAT AGT AAC GAT GTT GAT Thr Asn Glu Arg Thr Arg Gly Thr Ala Ile Asp Ser Asn Asp Val Asp 785 790 795 800	2400
TGT GAA CCT ATC ATA ACC TAT TCT AAT ATA GGT GTT TGT AAA AAT GGA Cys Glu Pro Ile Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn Gly 805 810 815	2448
GCT TTG GTT TTT ATT AAC GTC ACA CAT TCT GAT GGA GAC GTT CAA CCA Ala Leu Val Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln Pro 820 825 830	2496
ATT AGC ACC GGT AAT GTC ACG ATA CCT ACA AAT TTT ACC ATA TCT GTG Ile Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser Val 835 840 845	2544
CAA GTT GAG TAC ATT CAG GTT TAC ACT ACA CCG GTG TCA ATA GAT TGT Gln Val Glu Tyr Ile Gln Val Tyr Thr Thr Pro Val Ser Ile Asp Cys 850 855 860	2592
TCA AGG TAC GTT TGC AAT GGT AAC CCT AGA TGC AAT AAA TTG TTA ACG Ser Arg Tyr Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu Thr 865 870 875 880	2640
CAA TAC GTT TCT GCA TGT CAA ACT ATT GAG CAA GCA CTT GCA ATG GGT Gln Tyr Val Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met Gly 885 890 895	2688
GCC AGA CTT GAA AAC ATG GAG ATT GAT TCC ATG TTG TTT GTT TCG GAA Ala Arg Leu Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser Glu 900 905 910	2736
AAT GCC CTT AAA TTG GCA TCT GTT GAA GCA TTC AAT AGT ACG GAA ACT Asn Ala Leu Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr 915 920 925	2784
TTA GAT CCT ATT TAC AAA GAA TGG CCT AAC ATT GGT GGT TCT TGG CTA Leu Asp Pro Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu 930 935 940	2832
GGA GGT TTA AAA GAC ATA TTG CCA TCT CAC AAC AGC AAA CGT AAG TAC Gly Gly Leu Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys Tyr 945 950 955 960	2880
CGG TCG GCT ATA GAA GAT TTG CTT TTT GAT AAG GTT GTC ACA TCT GGC Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser Gly 965 970 975	2928
TTA GGT ACA GTT GAT GAA GAT TAT AAA CGT TGT ACA GGT GGT TAT GAC Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp 980 985 990	2976

ATA GCT GAC TTA GTG TGT GCA CAA TAT TAC AAT GGC ATC ATG GTG CTA Ile Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu 995 1000 1005	3024
CCT GGT GTA GCT AAT GAT GAC AAG ATG GCT ATG TAC ACT GCA TCT CTT Pro Gly Val Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser Leu 1010 1015 1020	3072
GCA GGT GGT ATA ACA TTA GGT GCA CTT GGT GGC GCA GTG TCT ATA Ala Gly Gly Ile Thr Leu Gly Ala Leu Gly Gly Ala Val Ser Ile 1025 1030 1035 1040	3120
CCT TTT GCA ATA GCA GTT CAA GCC AGA CTT AAT TAT GTT GCT CTA CAA Pro Phe Ala Ile Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln 1045 1050 1055	3168
ACT GAT GTA TTG AGC AAG AAC CAG CAG ATC CTG GCT AAT GCT TTC AAT Thr Asp Val Leu Ser Lys Asn Gln Ile Leu Ala Asn Ala Phe Asn 1060 1065 1070	3216
CAA GCT ATT GGT AAC ATT ACA CAG GCA TTT GGT AAG GTT AAT GAT GCT Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe Gly Lys Val Asn Asp Ala 1075 1080 1085	3264
ATA CAT CAA ACG TCA CAA GGT CTT GCT ACT GTT GCT AAA GCA TTG GCA Ile His Gln Thr Ser Gln Gly Leu Ala Thr Val Ala Lys Ala Leu Ala 1090 1095 1100	3312
AAA GTG CAA GAT GTT AAC ACA CAA GGG CAA GCT TTA AGC CAC CTA Lys Val Gln Asp Val Val Asn Thr Gln Gly Gln Ala Leu Ser His Leu 1105 1110 1115 1120	3360
ACA GTA CAA TTG CAA AAT AAT TTC CAA GCC ATT AGT AGT TCC ATT AGT Thr Val Gln Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile Ser 1125 1130 1135	3408
GAC ATT TAT AAC AGG CTT GAT GAA TTG AGT GCT GAT GCA CAA GTT GAC Asp Ile Tyr Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln Val Asp 1140 1145 1150	3456
AGG CTG ATT ACA GGA AGA CTT ACA GCA CTT AAT GCA TTT GTG TCT CAG Arg Leu Ile Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe Val Ser Gln 1155 1160 1165	3504
ACT TTA ACC AGA CAA GCA GAG GTT AGG GCT AGC AGA CAG CTT GCT AAA Thr Leu Thr Arg Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala Lys 1170 1175 1180	3552
GAC AAG GTA AAT GAA TGC GTT AGG TCT CAA TCT CAG AGA TTT GGA TTC Asp Lys Val Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly Phe 1185 1190 1195 1200	3600
TGT GGT AAT GGT ACA CAT TTA TTT TCA CTT GCA AAT GCA GCA CCA AAT Cys Gly Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro Asn 1205 1210 1215	3648
GGC ATG ATC TTC TTT CAC ACA GTG CTA TTA CCA ACA GCT TAT GAA ACC Gly Met Ile Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu Thr 1220 1225 1230	3696
G TG ACG GCC TGG TCA GGT ATT TGT GCA TCA GAT GGC GAT CGT ACT TTT Val Thr Ala Trp Ser Gly Ile Cys Ala Ser Asp Gly Asp Arg Thr Phe 1235 1240 1245	3744

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GGA CTT GTT GTT AAG GAT GTC CAG TTG ACG CTG TTT CGC AAT CTA GAT	3792
Gly Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu Asp	
1250 1255 1260	
GAC AAA TTC TAT TTG ACT CCC AGA ACT ATG TAT CAG CCT AGA GTT GCA	3840
Asp Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val Ala	
1265 1270 1275 1280	
ACT ACT TCT GAT TTT GTT CAA ATT GAA GGA TGT GAT GTG TTG TTT GTT	3888
Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe Val	
1285 1290 1295	
AAT GCA ACT GTA ATT GAC TTG CCT AGT ATT ATA CCT GAC TAT ATT GAT	3936
Asn Ala Thr Val Ile Asp Leu Pro Ser Ile Ile Pro Asp Tyr Ile Asp	
1300 1305 1310	
ATT AAT CAA ACT GTT CAG GAC ATA TTA GAA AAT TTC AGA CCA AAT TGG	3984
Ile Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg Pro Asn Trp	
1315 1320 1325	
ACT GTA CCT GAG TTG CCA CTT GAC ATT TTC AAT GCA ACC TAC TTA AAC	4032
Thr Val Pro Glu Leu Pro Leu Asp Ile Phe Asn Ala Thr Tyr Leu Asn	
1330 1335 1340	
CTG ACT GGT GAA ATT AAT GAC TTA GAA TTT AGG TCA GAA AAG TTA CAT	4080
Leu Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu Lys Leu His	
1345 1350 1355 1360	
AAC ACC ACA GAA CTT GCT ATT CTC ATT GAT AAT ATT AAT AAC ACA	4128
Asn Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile Asn Asn Thr	
1365 1370 1375	
TTA GTC AAT CTT GAA TGG CTC AAT AGA ATT GAA ACT TAT GTA AAA TGG	4176
Leu Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr Val Lys Trp	
1380 1385 1390	
CCT TGG TAT GTG TGG CTA CTA ATT GGA TTA GTA GTA ATA TTC TGC ATA	4224
Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile Phe Cys Ile	
1395 1400 1405	
CCC ATA TTG CTA TTT TGT TGT AGC ACT GGT TGT TGT GGA TGT ATT	4272
Pro Ile Leu Leu Phe Cys Cys Cys Ser Thr Gly Cys Cys Gly Cys Ile	
1410 1415 1420	
GGG TGT TTA GGA AGC TGT TGT CAT TCC ATA TGT AGT AGA AGG CGA TTT	4320
Gly Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg Phe	
1425 1430 1435 1440	
GAA AGT TAT GAA CCA ATT GAA AAA GTG CAT GTC CAC TAA	4359
Glu Ser Tyr Glu Pro Ile Glu Lys Val His Val His	
1445 1450	

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1452 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ile Val Leu Val Thr Cys Leu Leu Phe Ser Tyr Asn Ser Val Ile
 1 5 10 15

Cys Thr Ser Asn Asn Asp Cys Val Gln Val Asn Val Thr Gln Leu Pro
 20 25 30

Gly Asn Glu Asn Ile Ile Lys Asp Phe Leu Phe His Thr Phe Lys Glu
 35 40 45

Glu Gly Ser Val Val Val Gly Gly Tyr Tyr Pro Thr Glu Val Trp Tyr
 50 55 60

Asn Cys Ser Arg Ser Ala Thr Thr Ala Tyr Lys Asp Phe Ser Asn
 65 70 75 80

Ile His Ala Phe Tyr Phe Asp Met Glu Ala Met Glu Asn Ser Thr Gly
 85 90 95

Asn Ala Arg Gly Lys Pro Leu Leu Val His Val His Gly Asp Pro Val
 100 105 110

Ser Ile Ile Ile Tyr Ile Ser Ala Tyr Arg Asp Asp Val Gln Gly Arg
 115 120 125

Pro Leu Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile Ile
 130 135 140

Asp Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu Gly
 145 150 155 160

Asp Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Gly Asn Gly Thr
 165 170 175

Lys Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr Ile
 180 185 190

Ser Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn Asn
 195 200 205

Val Thr Ile Leu Tyr Ser Arg Ser Ser Thr Ala Thr Trp Gln Lys Ser
 210 215 220

Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys Leu
 225 230 235 240

Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr Glu
 245 250 255

Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly Gly
 260 265 270

Tyr Ile Pro Asp Gly Phe Ser Phe Asn Asn Trp Phe Met Leu Thr Asn
 275 280 285

Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu Leu
 290 295 300

Val Asn Cys Leu Trp Pro Val Pro Ser Leu Gly Val Ala Ala Gln Glu
 305 310 315 320

41

Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser Leu
325 330 335

Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp
340 345 350

Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly
355 360 365

Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser
370 375 380

Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly Pro
385 390 395 400

Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu Gly
405 410 415

Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly His
420 425 430

Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp Cys
435 440 445

Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr Ile
450 455 460

Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr Ala
465 470 475 480

Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys Cys
485 490 495

Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala Ser
500 505 510

Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser Phe
515 520 525

Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys Arg
530 535 540

Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr Leu
545 550 555 560

Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn Gln
565 570 575

Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp Asp Asp
580 585 590

Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val Ile
595 600 605

Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr Leu
610 615 620

Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn Cys
625 630 635 640

Lys Phe Asp Val Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val Arg
645 650 655

42

Ser Leu Tyr Val Ile Tyr Glu Glu Gly Asp Asn Ile Val Gly Val Pro
 660 665 670
 Ser Asp Asn Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp Ser
 675 680 685
 Cys Thr Asp Tyr Asn Ile Tyr Gly Arg Thr Gly Val Gly Ile Ile Arg
 690 695 700
 Gln Thr Asn Ser Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu Ser
 705 710 715 720
 Gly Asp Leu Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr Ser
 725 730 735
 Val Thr Pro Cys Asp Val Ser Ala Gln Ala Ala Val Ile Asp Gly Ala
 740 745 750
 Ile Val Gly Ala Met Thr Ser Ile Asn Ser Glu Met Leu Gly Leu Thr
 755 760 765
 His Trp Thr Thr Pro Asn Phe Tyr Tyr Tyr Ser Ile Tyr Asn Tyr
 770 775 780
 Thr Asn Glu Arg Thr Arg Gly Thr Ala Ile Asp Ser Asn Asp Val Asp
 785 790 795 800
 Cys Glu Pro Ile Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn Gly
 805 810 815
 Ala Leu Val Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln Pro
 820 825 830
 Ile Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser Val
 835 840 845
 Gln Val Glu Tyr Ile Gln Val Tyr Thr Pro Val Ser Ile Asp Cys
 850 855 860
 Ser Arg Tyr Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu Thr
 865 870 875 880
 Gln Tyr Val Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met Gly
 885 890 895
 Ala Arg Leu Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser Glu
 900 905 910
 Asn Ala Leu Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr
 915 920 925
 Leu Asp Pro Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu
 930 935 940
 Gly Gly Leu Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys Tyr
 945 950 955 960
 Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser Gly
 965 970 975
 Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp
 980 985 990

Ile Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu
995 1000 1005

Pro Gly Val Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser Leu
1010 1015 1020

Ala Gly Gly Ile Thr Leu Gly Ala Leu Gly Gly Ala Val Ser Ile
1025 1030 1035 1040

Pro Phe Ala Ile Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln
1045 1050 1055

Thr Asp Val Leu Ser Lys Asn Gln Ile Leu Ala Asn Ala Phe Asn
1060 1065 1070

Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe Gly Lys Val Asn Asp Ala
1075 1080 1085

Ile His Gln Thr Ser Gln Gly Leu Ala Thr Val Ala Lys Ala Leu Ala
1090 1095 1100

Lys Val Gln Asp Val Val Asn Thr Gln Gly Gln Ala Leu Ser His Leu
1105 1110 1115 1120

Thr Val Gln Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile Ser
1125 1130 1135

Asp Ile Tyr Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln Val Asp
1140 1145 1150

Arg Leu Ile Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe Val Ser Gln
1155 1160 1165

Thr Leu Thr Arg Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala Lys
1170 1175 1180

Asp Lys Val Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly Phe
1185 1190 1195 1200

Cys Gly Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro Asn
1205 1210 1215

Gly Met Ile Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu Thr
1220 1225 1230

Val Thr Ala Trp Ser Gly Ile Cys Ala Ser Asp Gly Asp Arg Thr Phe
1235 1240 1245

Gly Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu Asp
1250 1255 1260

Asp Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val Ala
1265 1270 1275 1280

Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe Val
1285 1290 1295

Asn Ala Thr Val Ile Asp Leu Pro Ser Ile Ile Pro Asp Tyr Ile Asp
1300 1305 1310

Ile Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg Pro Asn Trp
1315 1320 1325

Thr Val Pro Glu Leu Pro Leu Asp Ile Phe Asn Ala Thr Tyr Leu Asn
 1330 1335 1340

Leu Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu Lys Leu His
 1345 1350 1355 1360

Asn Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile Asn Asn Thr
 1365 1370 1375

Leu Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr Val Lys Trp
 1380 1385 1390

Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile Phe Cys Ile
 1395 1400 1405

Pro Ile Leu Leu Phe Cys Cys Cys Ser Thr Gly Cys Cys Gly Cys Ile
 1410 1415 1420

Gly Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg Phe
 1425 1430 1435 1440

Glu Ser Tyr Glu Pro Ile Glu Lys Val His Val His
 1445 1450

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 201 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Gly Ser Val Val Val Gly Gly Tyr Tyr Pro Thr Glu Val Trp Tyr Asn
 1 5 10 15

Cys Ser Arg Ser Ala Thr Thr Ala Tyr Lys Asp Phe Ser Asn Ile
 20 25 30

His Ala Phe Tyr Phe Asp Met Glu Ala Met Glu Asn Ser Thr Gly Asn
 35 40 45

Ala Arg Gly Lys Pro Leu Leu Val His Val His Gly Asp Pro Val Ser
 50 55 60

Ile Ile Ile Tyr Ile Ser Ala Tyr Arg Asp Asp Val Gln Gly Arg Pro
 65 70 75 80

Leu Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile Ile Asp
 85 90 95

Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu Gly Asp
 100 105 110

Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Gly Asn Gly Thr Lys
 115 120 125

Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr Ile Ser
 130 135 140

45

Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn Asn Val
145 150 155 160

Thr Ile Leu Tyr Ser Arg Ser Ser Thr Ala Thr Trp Gln Lys Ser Ala
165 170 175

Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys Leu Asn
180 185 190

Asn Thr Asn Gly Leu Lys Ser Tyr Glu
195 200

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser Tyr Gly
1 5 10 15

Glu Ile Ser Phe Gly Val Thr Asp Gly Pro Arg Tyr Cys Tyr Ala Leu
20 25 30

Tyr Asn Gly Thr Ala Leu Lys Tyr Leu Gly Thr Leu Pro Pro Ser Val
35 40 45

Lys Glu Ile
50

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr Ile Ala
1 5 10 15

Tyr Thr Ser Tyr Thr
20

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Pro	Ile	Ala	Ser	Thr	Leu	Ser	Asn	Ile	Thr	Leu	Pro	Met	Gln	Asp	Asn
1				5					10				15		
Asn	Thr	Asp	Val	Tyr	Cys	Ile	Arg	Ser	Asn	Gln	Phe	Ser	Val	Tyr	Val
	20						25					30			
His	Ser	Thr	Cys	Lys	Ser	Ser	Leu	Trp	Asp	Asp	Val	Phe	Asn	Ser	Asp
	35					40					45				
Cys	Thr	Asp													
	50														

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Thr	Asn	Glu	Gln	Val	Val	Arg	Ser	Leu	Tyr	Val	Ile	Tyr	Glu	Glu	Gly
1				5					10			15			
Asp	Asn	Ile	Val	Gly	Val	Pro	Ser	Asp	Asn	Ser	Gly	Leu	His	Asp	Leu
	20					25					30				
Ser	Val	Leu	His	Leu	Asp	Ser	Cys	Thr	Asp	Tyr	Asn	Ile	Tyr	Gly	Arg
	35				40					45					
Thr	Gly	Val													
	50														

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 81 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Trp	Thr	Thr	Thr	Pro	Asn	Phe	Tyr	Tyr	Tyr	Ser	Ile	Tyr	Asn	Tyr	Thr
1				5				10				15			
Asn	Glu	Arg	Thr	Arg	Gly	Thr	Ala	Ile	Asp	Ser	Asn	Asp	Val	Asp	Cys
	20					25					30				
Glu	Pro	Ile	Ile	Thr	Tyr	Ser	Asn	Ile	Gly	Val	Cys	Lys	Asn	Gly	Ala
	35					40					45				
Leu	Val	Phe	Ile	Asn	Val	Thr	His	Ser	Asp	Gly	Asp	Val	Gln	Pro	Ile
	50				55					60					

47

Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser Val Gln
65 70 75 80
Val

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 126 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser Glu Asn Ala Leu
1 5 10 15

Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr Leu Asp Pro
20 25 30

Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu Gly Gly Leu
35 40 45

Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys Tyr Arg Ser Ala
50 55 60

Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser Gly Leu Gly Thr
65 70 75 80

Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp Ile Ala Asp
85 90 95

Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val
100 105 110

Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser Leu Ala
115 120 125

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 76 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe
1 5 10 15

Val Ser Gln Thr Leu Thr Arg Gln Ala Glu Val Arg Ala Ser Arg Gln
20 25 30

Leu Ala Lys Asp Lys Val Asn Glu Cys Val Arg Ser Gln Ser Gln Arg
35 40 45

48

Phe Gly Phe Cys Gly Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala
50 55 60

Ala Pro Asn Gly Met Ile Phe Phe His Thr Val Leu
65 70 75

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 203 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu Asp Asp
1 5 10 15

Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val Ala Thr
20 25 30

Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe Val Asn
35 40 45

Ala Thr Val Ile Asp Leu Pro Ser Ile Ile Pro Asp Tyr Ile Asp Ile
50 55 60

Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg Pro Asn Trp Thr
65 70 75 80

Val Pro Glu Leu Pro Leu Asp Ile Phe Asn Ala Thr Tyr Leu Asn Leu
85 90 95

Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu Lys Leu His Asn
100 105 110

Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile Asn Asn Thr Leu
115 120 125

Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr Val Lys Trp Pro
130 135 140

Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile Phe Cys Ile Pro
145 150 155 160

Ile Leu Leu Phe Cys Cys Cys Ser Thr Gly Cys Cys Gly Cys Ile Gly
165 170 175

Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg Phe Glu
180 185 190

Ser Tyr Glu Pro Ile Glu Lys Val His Val His
195 200

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asp Phe Leu Phe His Thr Phe Lys
1 5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Trp Tyr Asn Cys Ser Arg Ser Ala Thr Thr Thr Ala Tyr Lys Asp Phe
1 5 10 15
Ser Asn Ile

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Tyr Val Thr Ala Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr Glu
1 5 10 15

50

Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly Gly
20 25 30

Tyr Ile

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Ser Leu Asn Asn Thr Val Asp
1 5

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Gly Val Thr Asp Gly Pro Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr
1 5 10 15

Ala Leu Lys Tyr Leu Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala
20 25 30

Ile Ser

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr Ala Ile Lys Lys
1 5 10 15

Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile
20 25

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Ile Ser Val Gln Val Glu Tyr Ile Gln Val Tyr Thr Thr Pro Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr Leu Asp Pro
1 5 10 15

Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu Gly Gly Leu
20 25 30

Lys Asp Ile Leu Pro
35

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 78 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

52

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Ala Asn Ala Phe Asn Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe Gly
 1 5 10 15

Lys Val Asn Asp Ala Ile His Gln Thr Ser Gln Gly Leu Ala Thr Val
 20 25 30

Ala Lys Ala Leu Ala Lys Val Gln Asp Val Val Asn Thr Gln Gly Gln
 35 40 45

Ala Leu Ser His Leu Thr Val Gln Leu Gln Asn Asn Phe Gln Ala Ile
 50 55 60

Ser Ser Ser Ile Ser Asp Ile Tyr Asn Arg Leu Asp Glu Leu
 65 70 75

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Leu Ala Ile Leu Ile Asp Asn Ile Asn Asn Thr Leu Val Asn Leu Glu
 1 5 10 15

Trp Leu Asn Arg Ile Glu Thr Tyr Val Lys
 20 25

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 372 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..372

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CAA GGG CAA GCT TTA AGC CAC CTA ACA GTA CAA TTG CAA AAT AAT TTC
 Gln Gly Gln Ala Leu Ser His Leu Thr Val Gln Leu Gln Asn Asn Phe
 1 5 10 15 48

CAA GCC ATT AGT AGT TCC ATT AGT GAC ATT TAT AAC AGG CTT GAT GAA
 Gln Ala Ile Ser Ser Ile Ser Asp Ile Tyr Asn Arg Leu Asp Glu
 20 25 30 96

TTG AGT GCT GAT GCA CAA GTT GAC AGG CTG ATT ACA GGA AGA CTT ACA
 Leu Ser Ala Asp Ala Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Thr
 35 40 45 144

53

GCA CTT AAT GCA TTT GTG TCT CAG ACT TTA ACC AGA CAA GCA GAG GTT	192
Ala Leu Asn Ala Phe Val Ser Gln Thr Leu Thr Arg Gln Ala Glu Val	
50 55 60	
AGG GCT AGC AGA CAG CTT GCT AAA GAC AAG GTA AAT GAA TGC GTT AGG	240
Arg Ala Ser Arg Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Arg	
65 70 75 80	
TCT CAA TCT CAG AGA TTT GGA TTC TGT GGT AAT GGT ACA CAT TTA TTT	288
Ser Gln Ser Gln Arg Phe Gly Phe Cys Gly Asn Gly Thr His Leu Phe	
85 90 95	
TCA CTT GCA AAT GCA GCA CCA AAT GGC ATG ATC TTC TTT CAC ACA GTG	336
Ser Leu Ala Asn Ala Ala Pro Asn Gly Met Ile Phe Phe His Thr Val	
100 105 110	
CTA TTA CCA ACA GCT TAT GAA ACC GTG ACG GCC TGG	372
Leu Leu Pro Thr Ala Tyr Glu Thr Val Thr Ala Trp	
115 120	

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 124 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Gln Gly Gln Ala Leu Ser His Leu Thr Val Gln Leu Gln Asn Asn Phe	
1 5 10 15	
Gln Ala Ile Ser Ser Ser Ile Ser Asp Ile Tyr Asn Arg Leu Asp Glu	
20 25 30	
Leu Ser Ala Asp Ala Gln Val Asp Arg Leu Ile Thr Gly Arg Leu Thr	
35 40 45	
Ala Leu Asn Ala Phe Val Ser Gln Thr Leu Thr Arg Gln Ala Glu Val	
50 55 60	
Arg Ala Ser Arg Gln Leu Ala Lys Asp Lys Val Asn Glu Cys Val Arg	
65 70 75 80	
Ser Gln Ser Gln Arg Phe Gly Phe Cys Gly Asn Gly Thr His Leu Phe	
85 90 95	
Ser Leu Ala Asn Ala Ala Pro Asn Gly Met Ile Phe Phe His Thr Val	
100 105 110	
Leu Leu Pro Thr Ala Tyr Glu Thr Val Thr Ala Trp	
115 120	

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 180 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown

54

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..180

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CTT GGT ATG AAG CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	48
Leu Gly Met Lys Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu	
1 5 10 15	
AGT AAC ATC ACA CTA CCA ATG CAG GAT AAT AAC ACC GAT GTG TAC TGC	96
Ser Asn Ile Thr Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys	
20 25 30	
ATT CGT TCT AAC CAA TTT TCA GTT TAC GTT CAT TCC ACT TGT AAA AGT	144
Ile Arg Ser Asn Gln Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser	
35 40 45	
TCT TTA TGG GAC GAT GTG TTT AAT TCC GAC TGC ACA	180
Ser Leu Trp Asp Asp Val Phe Asn Ser Asp Cys Thr	
50 55 60	

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 60 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Leu Gly Met Lys Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu	
1 5 10 15	
Ser Asn Ile Thr Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys	
20 25 30	
Ile Arg Ser Asn Gln Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser	
35 40 45	
Ser Leu Trp Asp Asp Val Phe Asn Ser Asp Cys Thr	
50 55 60	

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 141 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..141

55

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GTC ATT AGA TTC AAC CTT AAT TTT ACC ACA GAT GTA CAA TCT GGT ATG	48
Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp Val Gln Ser Gly Met	
1 5 10 15	
GGT GCT ACA GTA TTT TCA CTG AAT ACA ACA GGT GGT GTC ATT CTT GAG	96
Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly Gly Val Ile Leu Glu	
20 25 30	
ATT TCT TGT TAT AAT GAT ACA GTG AGT GAG TCA AGT TTC TAC AGT	141
Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser	
35 40 45	

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp Val Gln Ser Gly Met	
1 5 10 15	
Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly Gly Val Ile Leu Glu	
20 25 30	
Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser	
35 40 45	

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..51

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

TGT ATA ACT AAA AAT AAA ATC ATT GAC TAT AAC ACG TTT ACC AGC GCA	48
Cys Ile Thr Lys Asn Lys Ile Ile Asp Tyr Asn Thr Phe Thr Ser Ala	
1 5 10 15	
CAG	
Gln	51

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Cys Ile Thr Lys Asn Lys Ile Ile Asp Tyr Asn Thr Phe Thr Ser Ala
1 5 10 15

Gln

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..42

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TCT TGT TAT AAT GAT ACA GTG AGT GAG TCA AGT TTC TAC AGT
Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser
1 5 10

42

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser Ser Phe Tyr Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

57

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..51

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

ATT GGG TGT TTA GGA AGC TGT TGT CAT TCC ATA TGT AGT AGA AGG CGA
Ile Gly Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg
1 5 10 15

48

TTT
Phe

51

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Ile Gly Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..42

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

TGC ATA CCC ATA TTG CTA TTT TGT TGT TGT AGC ACT GGT TGT
Cys Ile Pro Ile Leu Leu Phe Cys Cys Ser Thr Gly Cys
1 5 10

42

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Cys Ile Pro Ile Leu Leu Phe Cys Cys Cys Ser Thr Gly Cys
 1 5 10

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 195 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 1..195

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TAC TTA AAC CTG ACT GGT GAA ATT AAT GAC TTA GAA TTT AGG TCA GAA 48
 Tyr Leu Asn Leu Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu
 1 5 10 15

AAG TTA CAT AAC ACC ACA GTA GAA CTT GCT ATT CTC ATT GAT AAT ATT 96
 Lys Leu His Asn Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile
 20 25 30

AAT AAC ACA TTA GTC AAT CTT GAA TGG CTC AAT AGA ATT GAA ACT TAT 144
 Asn Asn Thr Leu Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr
 35 40 45

GTA AAA TGG CCT TGG TAT GTG TGG CTA CTA ATT GGA TTA GTA ATA 192
 Val Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile
 50 55 60

TTC 195
 Phe
 65

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 65 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Tyr Leu Asn Leu Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu
 1 5 10 15

Lys Leu His Asn Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile
 20 25 30

Asn Asn Thr Leu Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr
 35 40 45

59

Val Lys Trp Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile
 50 55 60

Phe
 65

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 765 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..765

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAT GGA CCG CGT TAC TGT TAC GCA CTC TAT AAT GGC ACG GCT CTT AAG Asp Gly Pro Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys 1 5 10 15	48
TAT TTA GGA ACA TTA CCA CCT AGT GTC AAG GAA ATT GCT ATT AGT AAG Tyr Leu Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys 20 25 30	96
TGG GGC CAT TTT TAT ATT AAT GGT TAC AAT TTC TTT AGC ACT TTT CCT Trp Gly His Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro 35 40 45	144
ATT GAT TGT ATA TCT TTT AAT TTA ACC ACT GGT GAT AGT GGA GCA TTT Ile Asp Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe 50 55 60	192
TGG ACA ATT GCT TAC ACA TCG TAC ACT GAC GCA TTA GTA CAA GTT GAA Trp Thr Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu 65 70 75 80	240
AAC ACA GCT ATT AAA AAG GTG ACG TAT TGT AAC AGT CAC ATT AAT AAC Asn Thr Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn 85 90 95	288
ATT AAA TGT TCT CAA CTT ACT GCT AAT TTG CAA AAT GGA TTT TAT CCT Ile Lys Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro 100 105 110	336
GTT GCT TCA AGT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA Val Ala Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu 115 120 125	384
CCT AGT TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT Pro Ser Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly 130 135 140	432
ATG AAG CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA AGT AAC Met Lys Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn 145 150 155 160	480

60

ATC	ACA	CTA	CCA	ATG	CAG	GAT	AAT	AAC	ACC	GAT	GTG	TAC	TGC	ATT	CGT	528
Ile	Thr	Leu	Pro	Met	Gln	Asp	Asn	Asn	Thr	Asp	Val	Tyr	Cys	Ile	Arg	
				165					170					175		
TCT	AAC	CAA	TTT	TCA	GTT	TAC	GTT	CAT	TCC	ACT	TGT	AAA	AGT	TCT	TTA	576
Ser	Asn	Gln	Phe	Ser	Val	Tyr	Val	His	Ser	Thr	Cys	Lys	Ser	Ser	Leu	
			180					185				190				
TGG	GAC	GAT	GTG	TTT	AAT	TCC	GAC	TGC	ACA	GAT	GTT	TTA	TAT	GCT	ACA	624
Trp	Asp	Asp	Val	Phe	Asn	Ser	Asp	Cys	Thr	Asp	Val	Leu	Tyr	Ala	Thr	
			195				200				205					
GCT	GTT	ATA	AAA	ACT	GGT	ACT	TGT	CCT	TTC	TCG	TTT	GAT	AAA	TTG	AAC	672
Ala	Val	Ile	Lys	Thr	Gly	Thr	Cys	Pro	Phe	Ser	Phe	Asp	Lys	Leu	Asn	
			210			215				220						
AAT	TAC	TTA	ACT	TTT	AAC	AAG	TTC	TGT	TTG	TCA	TTG	AAT	CCT	GTT	GGT	720
Asn	Tyr	Leu	Thr	Phe	Asn	Lys	Phe	Cys	Leu	Ser	Leu	Asn	Pro	Val	Gly	
			225			230			235			240				
GCC	AAC	TGC	AAG	TTT	GAT	GTT	GCC	GCT	CGT	ACA	AGA	ACC	AAT	GAG	765	
Ala	Asn	Cys	Lys	Phe	Asp	Val	Ala	Ala	Arg	Thr	Arg	Thr	Asn	Glu		
			245					250				255				

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 255 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

Asp Gly Pro Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys
1 5 10 15

Tyr Leu Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys
20 25 30

Trp Gly His Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro
35 40 45

Ile Asp Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe
50 55 60

Trp Thr Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu
65 70 75 80

Asn Thr Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn
85 90 95

Ile Lys Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro
100 105 110

Pro Ser Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly
130 135 140

61

Met Lys Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn
 145 150 155 160

Ile Thr Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg
 165 170 175

Ser Asn Gln Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu
 180 185 190

Trp Asp Asp Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr
 195 200 205

Ala Val Ile Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn
 210 215 220

Asn Tyr Leu Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly
 225 230 235 240

Ala Asn Cys Lys Phe Asp Val Ala Ala Arg Thr Arg Thr Asn Glu
 245 250 255

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1284 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1284

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

AGG CCT CTT TTA AAA CAT GGT TTG TTG TGT ATA ACT AAA AAT AAA ATC	48
Arg Pro Leu Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile	
1 5 10 15	
ATT GAC TAT AAC ACG TTT ACC AGC GCA CAG TGG AGT GCC ATA TGT TTG	96
Ile Asp Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu	
20 25 30	
GGT GAT GAC AGA AAA ATA CCA TTC TCT GTC ATA CCC ACA GGT AAT GGT	144
Gly Asp Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Gly Asn Gly	
35 40 45	
ACA AAA ATA TTT GGT CTT GAG TGG AAT GAT GAC TAT GTT ACA GCC TAT	192
Thr Lys Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr	
50 55 60	
ATT AGT GAT CGT TCT CAC CAT TTG AAC ATC AAT AAT TGG TTT AAC	240
Ile Ser Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn	
65 70 75 80	
AAT GTG ACA ATC CTA TAC TCT CGA TCA AGC ACT GCT ACG TGG CAG AAG	288
Asn Val Thr Ile Leu Tyr Ser Arg Ser Ser Thr Ala Thr Trp Gln Lys	
85 90 95	

AGT GCT GCA TAT GTT TAT CAA GGT GTT TCA AAT TTT ACT TAT TAC AAG Ser Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys 100 105 110	336
TTA AAT AAC ACC AAT GGC TTG AAA AGC TAT GAA TTG TGT GAA GAT TAT Leu Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr 115 120 125	384
GAA TGC TGC ACT GGC TAT GCT ACC AAC GTA TTT GCC CCG ACA GTG GGC Glu Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly 130 135 140	432
GGT TAT ATA CCT GAT GGC TTC AGT TTT AAC AAT TGG TTT ATG CTT ACA Gly Tyr Ile Pro Asp Gly Phe Ser Phe Asn Asn Trp Phe Met Leu Thr 145 150 155 160	480
AAC AGT TCC ACG TTT GTT AGT GGC AGA TTT GTA ACA AAT CAA CCA TTA Asn Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu 165 170 175	528
TTG GTT AAT TGT TTG TGG CCA GTG CCC AGT CTT GGT GTC GCA GCA CAA Leu Val Asn Cys Leu Trp Pro Val Pro Ser Leu Gly Val Ala Ala Gln 180 185 190	576
GAA TTT TGT TTT GAA GGT GCG CAG TTT AGC CAA TGT AAT GGT GTG TCT Glu Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser 195 200 205	624
TTA AAC AAT ACA GTG GAT GTC ATT AGA TTC AAC CTT AAT TTT ACC ACA Leu Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr 210 215 220	672
GAT GTA CAA TCT GGT ATG GGT GCT ACA GTA TTT TCA CTG AAT ACA ACA Asp Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr 225 230 235 240	720
GGT GGT GTC ATT CTT GAG ATT TCT TGT TAT AAT GAT ACA GTG AGT GAG Gly Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu 245 250 255	768
TCA AGT TTC TAC AGT TAT GGT GAA ATT TCA TTC GGC GTA ACT GAT GGA Ser Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly 260 265 270	816
CCG CGT TAC TGT TAC GCA CTC TAT AAT GGC ACG GCT CTT AAG TAT TTA Pro Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu 275 280 285	864
GGA ACA TTA CCA CCT AGT GTC AAG GAA ATT GCT ATT AGT AAG TGG GGC Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly 290 295 300	912
CAT TTT TAT ATT AAT GGT TAC AAT TTC TTT AGC ACT TTT CCT ATT GAT His Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp 305 310 315 320	960
TGT ATA TCT TTT AAT TTA ACC ACT GGT GAT AGT GGA GCA TTT TGG ACA Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr 325 330 335	1008
ATT GCT TAC ACA TCG TAC ACT GAC GCA TTA GTA CAA GTT GAA AAC ACA Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr 340 345 350	1056

63

GCT ATT AAA AAG GTG ACG TAT TGT AAC AGT CAC ATT AAT AAC ATT AAA	1104																																		
Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys																																			
355	360	365		TGT TCT CAA CTT ACT GCT AAT TTG CAA AAT GGA TTT TAT CCT GTT GCT	1152	Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala		370	375	380		TCA ACT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA CCT AGT	1200	Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser		385	390	395	400	TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG AAG	1248	Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys		405	410	415		CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	1284	Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu		420	425		
365																																			
TGT TCT CAA CTT ACT GCT AAT TTG CAA AAT GGA TTT TAT CCT GTT GCT	1152																																		
Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala																																			
370	375	380		TCA ACT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA CCT AGT	1200	Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser		385	390	395	400	TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG AAG	1248	Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys		405	410	415		CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	1284	Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu		420	425										
380																																			
TCA ACT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA CCT AGT	1200																																		
Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser																																			
385	390	395	400	TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG AAG	1248	Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys		405	410	415		CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	1284	Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu		420	425																		
395	400																																		
TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG AAG	1248																																		
Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys																																			
405	410	415		CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	1284	Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu		420	425																										
415																																			
CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA	1284																																		
Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu																																			
420	425																																		

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 428 amino acids
- (B) TYPE: amino acid
- (C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Arg Pro Leu Leu Lys His Gly Leu Leu Cys Ile Thr Lys Asn Lys Ile			
1	5	10	15
Ile Asp Tyr Asn Thr Phe Thr Ser Ala Gln Trp Ser Ala Ile Cys Leu			
20	25	30	
Gly Asp Asp Arg Lys Ile Pro Phe Ser Val Ile Pro Thr Gly Asn Gly			
35	40	45	
Thr Lys Ile Phe Gly Leu Glu Trp Asn Asp Asp Tyr Val Thr Ala Tyr			
50	55	60	
Ile Ser Asp Arg Ser His His Leu Asn Ile Asn Asn Asn Trp Phe Asn			
65	70	75	80
Asn Val Thr Ile Leu Tyr Ser Arg Ser Ser Thr Ala Thr Trp Gln Lys			
85	90	95	
Ser Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys			
100	105	110	
Leu Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr			
115	120	125	
Glu Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly			
130	135	140	
Gly Tyr Ile Pro Asp Gly Phe Ser Phe Asn Asn Trp Phe Met Leu Thr			
145	150	155	160

64

Asn Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu
 165 170 175

Leu Val Asn Cys Leu Trp Pro Val Pro Ser Leu Gly Val Ala Ala Gln
 180 185 190

Glu Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser
 195 200 205

Leu Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr
 210 215 220

Asp Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr
 225 230 235 240

Gly Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu
 245 250 255

Ser Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly
 260 265 270

Pro Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu
 275 280 285

Gly Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly
 290 295 300

His Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp
 305 310 315 320

Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr
 325 330 335

Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr
 340 345 350

Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys
 355 360 365

Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala
 370 375 380

Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser
 385 390 395 400

Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys
 405 410 415

Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu
 420 425

(2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 546 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: double
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

65

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..546

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAT TGT ATA TCT TTT AAT TTA ACC ACT GGT GAT AGT GGA GCA TTT TGG	48
Asp Cys Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp	
1 5 10 15	
ACA ATT GCT TAC ACA TCG TAC ACT GAC GCA TTA GTA CAA GTT GAA AAC	96
Thr Ile Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn	
20 25 30	
ACA GCT ATT AAA AAG GTG ACG TAT TGT AAC AGT CAC ATT AAT AAC ATT	144
Thr Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile	
35 40 45	
AAA TGT TCT CAA CTT ACT GCT AAT TTG CAA AAT GGA TTT TAT CCT GTT	192
Lys Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val	
50 55 60	
GCT TCA AGT GAA GTT GGT CTT GTC AAT AAG AGT GTT GTG TTA CTA CCT	240
Ala Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro	
65 70 75 80	
AGT TTC TAT TCA CAT ACC AGT GTT AAT ATA ACT ATT GAT CTT GGT ATG	288
Ser Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met	
85 90 95	
AAG CGT AGT GGT TAT GGT CAA CCC ATA GCC TCA ACA TTA AGT AAC ATC	336
Lys Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile	
100 105 110	
ACA CTA CCA ATG CAG GAT AAT AAC ACC GAT GTG TAC TGC ATT CGT TCT	384
Thr Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser	
115 120 125	
AAC CAA TTT TCA GTT TAC GTT CAT TCC ACT TGT AAA AGT TCT TTA TGG	432
Asn Gln Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp	
130 135 140	
GAC GAT GTG TTT AAT TCC GAC TGC ACA GAT GTT TTA TAT GCT ACA GCT	480
Asp Asp Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala	
145 150 155 160	
GTT ATA AAA ACT GGT ACT TGT CCT TTC TCG TTT GAT AAA TTG AAC AAT	528
Val Ile Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn	
165 170 175	
TAC TTA ACT TTT AAC AAG	546
Tyr Leu Thr Phe Asn Lys	
180	

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

66

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Asp	Cys	Ile	Ser	Phe	Asn	Leu	Thr	Thr	Gly	Asp	Ser	Gly	Ala	Phe	Trp
1				5				10					15		
Thr	Ile	Ala	Tyr	Thr	Ser	Tyr	Thr	Asp	Ala	Leu	Val	Gln	Val	Glu	Asn
			20				25					30			
Thr	Ala	Ile	Lys	Lys	Val	Thr	Tyr	Cys	Asn	Ser	His	Ile	Asn	Asn	Ile
			35			40					45				
Lys	Cys	Ser	Gln	Leu	Thr	Ala	Asn	Leu	Gln	Asn	Gly	Phe	Tyr	Pro	Val
			50			55			60						
Ala	Ser	Ser	Glu	Val	Gly	Leu	Val	Asn	Lys	Ser	Val	Val	Leu	Leu	Pro
			65			70			75			80			
Ser	Phe	Tyr	Ser	His	Thr	Ser	Val	Asn	Ile	Thr	Ile	Asp	Leu	Gly	Met
			85			90				95					
Lys	Arg	Ser	Gly	Tyr	Gly	Gln	Pro	Ile	Ala	Ser	Thr	Leu	Ser	Asn	Ile
			100			105					110				
Thr	Leu	Pro	Met	Gln	Asp	Asn	Asn	Thr	Asp	Val	Tyr	Cys	Ile	Arg	Ser
			115			120				125					
Asn	Gln	Phe	Ser	Val	Tyr	Val	His	Ser	Thr	Cys	Lys	Ser	Ser	Leu	Trp
			130			135			140						
Asp	Asp	Val	Phe	Asn	Ser	Asp	Cys	Thr	Asp	Val	Leu	Tyr	Ala	Thr	Ala
			145			150			155			160			
Val	Ile	Lys	Thr	Gly	Thr	Cys	Pro	Phe	Ser	Phe	Asp	Lys	Leu	Asn	Asn
			165			170				175					
Tyr	Leu	Thr	Phe	Asn	Lys										
			180												

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TAAATAGGCC TTTAGTGGAC ATGCACTTTT TCAATTGG

38

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

67

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TTAGTAGGCC TGTGAGGCT ATGGGTTGAC CATAACCAC

39

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CAGATCCCCG GTGTACAATC TGGTATGGGT GCTACAG

37

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

GTGCCCGG GTATGATTGT GCTCGTAAC TGCCTCTTG

39

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

AGCACCCATA CCAGATTGTA CATCTGCAGT GAAATTAAGA TTG

43

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 128 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Met	Ile	Val	Leu	Val	Thr	Cys	Leu	Leu	Phe	Ser	Tyr	Asn	Ser	Val	Ile
1						5			10						15
Cys	Thr	Ser	Asn	Asn	Asp	Cys	Val	Gln	Val	Asn	Val	Thr	Gln	Leu	Pro
			20					25				30			
Gly	Asn	Glu	Asn	Ile	Ile	Lys	Asp	Phe	Leu	Phe	His	Thr	Phe	Lys	Glu
				35			40				45				
Glu	Gly	Ser	Val	Val	Val	Gly	Gly	Tyr	Tyr	Pro	Thr	Glu	Val	Trp	Tyr
				50			55			60					
Asn	Cys	Ser	Arg	Ser	Ala	Thr	Thr	Ala	Tyr	Lys	Asp	Phe	Ser	Asn	
					70				75					80	
Ile	His	Ala	Phe	Tyr	Phe	Asp	Met	Glu	Ala	Met	Glu	Asn	Ser	Thr	Gly
				85				90				95			
Asn	Ala	Arg	Gly	Lys	Pro	Leu	Leu	Val	His	Val	His	Gly	Asp	Pro	Val
				100			105				110				
Ser	Ile	Ile	Ile	Tyr	Ile	Ser	Ala	Tyr	Arg	Asp	Asp	Val	Gln	Gly	Arg
				115			120					125			

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1101 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Asp	Val	Gln	Ser	Gly	Met	Gly	Ala	Thr	Val	Phe	Ser	Leu	Asn	Thr	Thr
1					5				10					15	
Gly	Gly	Val	Ile	Leu	Glu	Ile	Ser	Cys	Tyr	Asn	Asp	Thr	Val	Ser	Glu
			20				25					30			
Ser	Ser	Phe	Tyr	Ser	Tyr	Gly	Glu	Ile	Ser	Phe	Gly	Val	Thr	Asp	Gly
			35				40				45				
Pro	Arg	Tyr	Cys	Tyr	Ala	Leu	Tyr	Asn	Gly	Thr	Ala	Leu	Lys	Tyr	Leu
			50			55				60					
Gly	Thr	Leu	Pro	Pro	Ser	Val	Lys	Glu	Ile	Ala	Ile	Ser	Lys	Trp	Gly
			65			70			75			80			
His	Phe	Tyr	Ile	Asn	Gly	Tyr	Asn	Phe	Phe	Ser	Thr	Phe	Pro	Ile	Asp
			85					90			95				
Cys	Ile	Ser	Phe	Asn	Leu	Thr	Thr	Gly	Asp	Ser	Gly	Ala	Phe	Trp	Thr
			100			105					110				
Ile	Ala	Tyr	Thr	Ser	Tyr	Thr	Asp	Ala	Leu	Val	Gln	Val	Glu	Asn	Thr
			115			120					125				

69

Ala Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys
130 135 140

Cys Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala
145 150 155 160

Ser Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser
165 170 175

Phe Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys
180 185 190

Arg Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr
195 200 205

Leu Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn
210 215 220

Gln Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp Asp
225 230 235 240

Asp Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val
245 250 255

Ile Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr
260 265 270

Leu Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn
275 280 285

Cys Lys Phe Asp Val Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val
290 295 300

Arg Ser Leu Tyr Val Ile Tyr Glu Glu Gly Asp Asn Ile Val Gly Val
305 310 315 320

Pro Ser Asp Asn Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp
325 330 335

Ser Cys Thr Asp Tyr Asn Ile Tyr Gly Arg Thr Gly Val Gly Ile Ile
340 345 350

Arg Gln Thr Asn Ser Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu
355 360 365

Ser Gly Asp Leu Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr
370 375 380

Ser Val Thr Pro Cys Asp Val Ser Ala Gln Ala Ala Val Ile Asp Gly
385 390 395 400

Ala Ile Val Gly Ala Met Thr Ser Ile Asn Ser Glu Met Leu Gly Leu
405 410 415

Thr His Trp Thr Thr Pro Asn Phe Tyr Tyr Tyr Ser Ile Tyr Asn
420 425 430

Tyr Thr Asn Glu Arg Thr Arg Gly Thr Ala Ile Asp Ser Asn Asp Val
435 440 445

Asp Cys Glu Pro Ile Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn
450 455 460

70

Gly Ala Leu Val Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln
 465 470 475 480
 Pro Ile Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser
 485 490 495
 Val Gln Val Glu Tyr Ile Gln Val Tyr Thr Thr Pro Val Ser Ile Asp
 500 505 510
 Cys Ser Arg Tyr Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu
 515 520 525
 Thr Gln Tyr Val Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met
 530 535 540
 Gly Ala Arg Leu Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser
 545 550 555 560
 Glu Asn Ala Leu Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu
 565 570 575
 Thr Leu Asp Pro Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp
 580 585 590
 Leu Gly Gly Leu Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys
 595 600 605
 Tyr Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser
 610 615 620
 Gly Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr
 625 630 635 640
 Asp Ile Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val
 645 650 655
 Leu Pro Gly Val Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser
 660 665 670
 Leu Ala Gly Gly Ile Thr Leu Gly Ala Leu Gly Gly Ala Val Ser
 675 680 685
 Ile Pro Phe Ala Ile Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu
 690 695 700
 Gln Thr Asp Val Leu Ser Lys Asn Gln Gln Ile Leu Ala Asn Ala Phe
 705 710 715 720
 Asn Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe Gly Lys Val Asn Asp
 725 730 735
 Ala Ile His Gln Thr Ser Gln Gly Leu Ala Thr Val Ala Lys Ala Leu
 740 745 750
 Ala Lys Val Gln Asp Val Val Asn Thr Gln Gly Gln Ala Leu Ser His
 755 760 765
 Leu Thr Val Gln Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile
 770 775 780
 Ser Asp Ile Tyr Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln Val
 785 790 795 800

71

Asp Arg Leu Ile Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe Val Ser
 805 810 815
 Gln Thr Leu Thr Arg Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala
 820 825 830
 Lys Asp Lys Val Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly
 835 840 845
 Phe Cys Gly Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro
 850 855 860
 Asn Gly Met Ile Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu
 865 870 875 880
 Thr Val Thr Ala Trp Ser Gly Ile Cys Ala Ser Asp Gly Asp Arg Thr
 885 890 895
 Phe Gly Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu
 900 905 910
 Asp Asp Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val
 915 920 925
 Ala Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe
 930 935 940
 Val Asn Ala Thr Val Ile Asp Leu Pro Ser Ile Ile Pro Asp Tyr Ile
 945 950 955 960
 Asp Ile Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg Pro Asn
 965 970 975
 Trp Thr Val Pro Glu Leu Pro Leu Asp Ile Phe Asn Ala Thr Tyr Leu
 980 985 990
 Asn Leu Thr Gly Glu Ile Asn Asp Leu Glu Phe Arg Ser Glu Lys Leu
 995 1000 1005
 His Asn Thr Thr Val Glu Leu Ala Ile Leu Ile Asp Asn Ile Asn Asn
 1010 1015 1020
 Thr Leu Val Asn Leu Glu Trp Leu Asn Arg Ile Glu Thr Tyr Val Lys
 1025 1030 1035 1040
 Trp Pro Trp Tyr Val Trp Leu Leu Ile Gly Leu Val Val Ile Phe Cys
 1045 1050 1055
 Ile Pro Ile Leu Leu Phe Cys Cys Ser Thr Gly Cys Cys Gly Cys
 1060 1065 1070
 Ile Gly Cys Leu Gly Ser Cys Cys His Ser Ile Cys Ser Arg Arg Arg
 1075 1080 1085
 Phe Glu Ser Tyr Glu Pro Ile Glu Lys Val His Val His
 1090 1095 1100

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 362 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met	Ile	Val	Leu	Val	Thr	Cys	Leu	Leu	Phe	Ser	Tyr	Asn	Ser	Val	Ile
1															15

Cys	Thr	Ser	Asn	Asn	Asp	Cys	Val	Gln	Val	Asn	Val	Thr	Gln	Leu	Pro

Gly	Asn	Glu	Asn	Ile	Ile	Lys	Asp	Phe	Leu	Phe	His	Thr	Phe	Lys	Glu

Glu	Gly	Ser	Val	Val	Val	Gly	Gly	Tyr	Tyr	Pro	Thr	Glu	Val	Trp	Tyr

Asn	Cys	Ser	Arg	Ser	Ala	Thr	Thr	Ala	Tyr	Lys	Asp	Phe	Ser	Asn	
65															80

Ile	His	Ala	Phe	Tyr	Phe	Asp	Met	Glu	Ala	Met	Glu	Asn	Ser	Thr	Gly

Asn	Ala	Arg	Gly	Lys	Pro	Leu	Leu	Val	His	Val	His	Gly	Asp	Pro	Val
100															

Ser	Ile	Ile	Ile	Tyr	Ile	Ser	Ala	Tyr	Arg	Asp	Asp	Val	Gln	Gly	Arg
115															

Pro	Leu	Leu	Lys	His	Gly	Leu	Leu	Cys	Ile	Thr	Lys	Asn	Lys	Ile	Ile
130															

Asp	Tyr	Asn	Thr	Phe	Thr	Ser	Ala	Gln	Trp	Ser	Ala	Ile	Cys	Leu	Gly
145															160

Asp	Asp	Arg	Lys	Ile	Pro	Phe	Ser	Val	Ile	Pro	Thr	Gly	Asn	Gly	Thr
165															175

Lys	Ile	Phe	Gly	Leu	Glu	Trp	Asn	Asp	Asp	Tyr	Val	Thr	Ala	Tyr	Ile
180															190

Ser	Asp	Arg	Ser	His	His	Leu	Asn	Ile	Asn	Asn	Asn	Trp	Phe	Asn	Asn
195															205

Val	Thr	Ile	Leu	Tyr	Ser	Arg	Ser	Ser	Thr	Ala	Thr	Trp	Gln	Lys	Ser
210															220

Ala	Ala	Tyr	Val	Tyr	Gln	Gly	Val	Ser	Asn	Phe	Thr	Tyr	Tyr	Lys	Leu
225															240

Asn	Asn	Thr	Asn	Gly	Leu	Lys	Ser	Tyr	Glu	Leu	Cys	Glu	Asp	Tyr	Glu
245															255

Cys	Cys	Thr	Gly	Tyr	Ala	Thr	Asn	Val	Phe	Ala	Pro	Thr	Val	Gly	Gly
260															270

Tyr	Ile	Pro	Asp	Gly	Phe	Ser	Phe	Asn	Asn	Trp	Phe	Met	Leu	Thr	Asn
275															285

Ser	Ser	Thr	Phe	Val	Ser	Gly	Arg	Phe	Val	Thr
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser Leu
325 330 335
Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp
340 345 350
Val Gln Ser Gly Met Gly Ala Thr Val Phe
355 360

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1101 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys Leu
1 5 10 15
Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu Leu Cys Glu Asp Tyr Glu
20 25 30
Cys Cys Thr Gly Tyr Ala Thr Asn Val Phe Ala Pro Thr Val Gly Gly
35 40 45
Tyr Ile Pro Asp Gly Phe Ser Phe Asn Asn Trp Phe Met Leu Thr Asn
50 55 60
Ser Ser Thr Phe Val Ser Gly Arg Phe Val Thr Asn Gln Pro Leu Leu
65 70 75 80
Val Asn Cys Leu Trp Pro Val Pro Ser Leu Gly Val Ala Ala Gln Glu
85 90 95
Phe Cys Phe Glu Gly Ala Gln Phe Ser Gln Cys Asn Gly Val Ser Leu
100 105 110
Asn Asn Thr Val Asp Val Ile Arg Phe Asn Leu Asn Phe Thr Thr Asp
115 120 125
Val Gln Ser Gly Met Gly Ala Thr Val Phe Ser Leu Asn Thr Thr Gly
130 135 140
Gly Val Ile Leu Glu Ile Ser Cys Tyr Asn Asp Thr Val Ser Glu Ser
145 150 155 160
Ser Phe Tyr Ser Tyr Gly Glu Ile Ser Phe Gly Val Thr Asp Gly Pro
165 170 175
Arg Tyr Cys Tyr Ala Leu Tyr Asn Gly Thr Ala Leu Lys Tyr Leu Gly
180 185 190
Thr Leu Pro Pro Ser Val Lys Glu Ile Ala Ile Ser Lys Trp Gly His
195 200 205
Phe Tyr Ile Asn Gly Tyr Asn Phe Phe Ser Thr Phe Pro Ile Asp Cys
210 215 220

Ile Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr Ile
 225 230 235 240
 Ala Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr Ala
 245 250 255
 Ile Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys Cys
 260 265 270
 Ser Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala Ser
 275 280 285
 Ser Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser Phe
 290 295 300
 Tyr Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys Arg
 305 310 315 320
 Ser Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr Leu
 325 330 335
 Pro Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn Gln
 340 345 350
 Phe Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp Asp Asp
 355 360 365
 Val Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val Ile
 370 375 380
 Lys Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr Leu
 385 390 395 400
 Thr Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn Cys
 405 410 415
 Lys Phe Asp Val Ala Ala Arg Thr Arg Thr Asn Glu Gln Val Val Arg
 420 425 430
 Ser Leu Tyr Val Ile Tyr Glu Glu Gly Asp Asn Ile Val Gly Val Pro
 435 440 445
 Ser Asp Asn Ser Gly Leu His Asp Leu Ser Val Leu His Leu Asp Ser
 450 455 460
 Cys Thr Asp Tyr Asn Ile Tyr Gly Arg Thr Gly Val Gly Ile Ile Arg
 465 470 475 480
 Gln Thr Asn Ser Thr Leu Leu Ser Gly Leu Tyr Tyr Thr Ser Leu Ser
 485 490 495
 Gly Asp Leu Leu Gly Phe Lys Asn Val Ser Asp Gly Val Ile Tyr Ser
 500 505 510
 Val Thr Pro Cys Asp Val Ser Ala Gln Ala Ala Val Ile Asp Gly Ala
 515 520 525
 Ile Val Gly Ala Met Thr Ser Ile Asn Ser Glu Met Leu Gly Leu Thr
 530 535 540
 His Trp Thr Thr Thr Pro Asn Phe Tyr Tyr Ser Ile Tyr Asn Tyr
 545 550 555 560

75

Thr Asn Glu Arg Thr Arg Gly Thr Ala Ile Asp Ser Asn Asp Val Asp
565 570 575

Cys Glu Pro Ile Ile Thr Tyr Ser Asn Ile Gly Val Cys Lys Asn Gly
580 585 590

Ala Leu Val Phe Ile Asn Val Thr His Ser Asp Gly Asp Val Gln Pro
595 600 605

Ile Ser Thr Gly Asn Val Thr Ile Pro Thr Asn Phe Thr Ile Ser Val
610 615 620

Gln Val Glu Tyr Ile Gln Val Tyr Thr Pro Val Ser Ile Asp Cys
625 630 635 640

Ser Arg Tyr Val Cys Asn Gly Asn Pro Arg Cys Asn Lys Leu Leu Thr
645 650 655

Gln Tyr Val Ser Ala Cys Gln Thr Ile Glu Gln Ala Leu Ala Met Gly
660 665 670

Ala Arg Leu Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser Glu
675 680 685

Asn Ala Leu Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr
690 695 700

Leu Asp Pro Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu
705 710 715 720

Gly Gly Leu Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys Tyr
725 730 735

Arg Ser Ala Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser Gly
740 745 750

Leu Gly Thr Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp
755 760 765

Ile Ala Asp Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu
770 775 780

Pro Gly Val Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser Leu
785 790 795 800

Ala Gly Gly Ile Thr Leu Gly Ala Leu Gly Gly Ala Val Ser Ile
805 810 815

Pro Phe Ala Ile Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln
820 825 830

Thr Asp Val Leu Ser Lys Asn Gln Gln Ile Leu Ala Asn Ala Phe Asn
835 840 845

Gln Ala Ile Gly Asn Ile Thr Gln Ala Phe Gly Lys Val Asn Asp Ala
850 855 860

Ile His Gln Thr Ser Gln Gly Leu Ala Thr Val Ala Lys Ala Leu Ala
865 870 875 880

Lys Val Gln Asp Val Val Asn Thr Gln Gly Gln Ala Leu Ser His Leu
885 890 895

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Thr Val Gln Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile Ser
 900 905 910

Asp Ile Tyr Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln Val Asp
 915 920 925

Arg Leu Ile Thr Gly Arg Leu Thr Ala Leu Asn Ala Phe Val Ser Gln
 930 935 940

Thr Leu Thr Arg Gln Ala Glu Val Arg Ala Ser Arg Gln Leu Ala Lys
 945 950 955 960

Asp Lys Val Asn Glu Cys Val Arg Ser Gln Ser Gln Arg Phe Gly Phe
 965 970 975

Cys Gly Asn Gly Thr His Leu Phe Ser Leu Ala Asn Ala Ala Pro Asn
 980 985 990

Gly Met Ile Phe Phe His Thr Val Leu Leu Pro Thr Ala Tyr Glu Thr
 995 1000 1005

Val Thr Ala Trp Ser Gly Ile Cys Ala Ser Asp Gly Asp Arg Thr Phe
 1010 1015 1020

Gly Leu Val Val Lys Asp Val Gln Leu Thr Leu Phe Arg Asn Leu Asp
 1025 1030 1035 1040

Asp Lys Phe Tyr Leu Thr Pro Arg Thr Met Tyr Gln Pro Arg Val Ala
 1045 1050 1055

Thr Ser Ser Asp Phe Val Gln Ile Glu Gly Cys Asp Val Leu Phe Val
 1060 1065 1070

Asn Ala Thr Val Ile Asp Leu Pro Ser Ile Ile Pro Asp Tyr Ile Asp
 1075 1080 1085

Ile Asn Gln Thr Val Gln Asp Ile Leu Glu Asn Phe Arg
 1090 1095 1100

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 701 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TCAACCATTA TTGGTTAATT GTTGTGGCC AGTGCCAGT CTTGGTGTG	60
ATTTGTTT GAAGGTGCGC AGTTAGCCA ATGTAATGGT GTGTCTTAA ACAATACAGT	120
GGATGTCATT AGATTCAACC TTAATTAC CACAGATGTA CAATCTGGTA TGGGTGCTAC	180
AGTATTTCA CTGAATACAA CAGGTGGTGT CATTCTTGAG ATTTCTTGTG ATAATGATAC	240
AGTGAGTGAG TCAAGTTCT ACAGTTATGG TGAAATTCA TTCGGCGTAA CTGATGGACC	300
GCGTTACTGT TACGCACTCT ATAATGGCAC GGCTCTTAAG TATTTAGGAA CATTACCACC	360

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TAGTGTCAAG GAAATTGCTA TTAGTAAGTG GGGCCATTT TATATTAATG GTTACAATT	420
CTTTAGCACT TTTCTTATTG ATTGTATATC TTTTAATTG ACCACTGGTG ATAGTGGAGC	480
ATTTGGACA ATTGCTTACA CATCGTACAC TGACGGATTA GTACAAGTTG AAAACACAGC	540
TATTAAAAAG GTGACGTATT GTAACAGTCA CATTAAAC ATTAAATGTT CTCAACTTAC	600
TGCTAATTG CAAAATGGAT TTTATCCTGT TGCTTCAAGT GAAGTTGGTC TTGTCAATAA	660
GAGTGTGTTG TTACTACCTA GTTTCTATTC ACATACCACT G	701

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1401 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

AGCACCGGTA ATGTCACGAT ACCTACAAAT TTTACCATAT CTGTGCAAGT TGAGTACATT	60
CAGGTTTACA CTACACCGGT GTCAATAGAT TGTTCAAGGT ACGTTGCAA TGGTAACCCT	120
AGATGCAATA AATTGTTAAC GCAATACGTT TCTGCATGTC AAACTATTGA GCAAGCACTT	180
GCAATGGGTG CCAGACTTGA AAACATGGAG ATTGATTCCA TGTTGTTGT TTCGGAAAAT	240
GCCCTTAAAT TGGCATCTGT TGAAGCATTG AATAGTACGG AAACTTTAGA TCCTATTTAC	300
AAAGAATGGC CTAACATGG TGGTTCTTGG CTAGGAGGTT TAAAAGACAT ATTGCCATCT	360
CACAACAGCA AACGTAAGTA CCGGTCGGCT ATAGAAGATT TGCTTTTGA TAAGGTTGTA	420
ACATCTGGCT TAGGTACAGT TGATGAAGAT TATAAACGTT GTACAGGTGG TTATGACATA	480
GCTGACTTAG TGTGTGCACA ATATTACAAT GGCATCATGG TGCTACCTGG TGTAGCTAAT	540
GATGACAAGA TGGCTATGTA CACTGCATCT CTTGCAGGTG GTATAACATT AGGTGCACCT	600
GGTGGTGGCG CAGTGTCTAT ACCTTTGCA ATAGCAGTTC AAGCCAGACT TAATTATGTT	660
GCTCTACAAA CTGATGTATT GAGCAAGAAC CAGCAGATCC TGGCTAATGC TTTCAATCAA	720
GCTATTGGTA ACATTACACA GGCATTTGGT AAGGTTAATG ATGCTATACA TCAAACGTCA	780
CAAGGTCTTG CTACTGTTGC TAAAGCATTG GCAAAAGTGC AAGATGTTGT TAACACACAA	840
GGGCAAGCTT TAAGCCACCT AACAGTACAA TTGCAAAATA ATTTCCAAGC CATTAGTAGT	900
TCCATTAGTG ACATTATCAA CAGGCTTGAT GAATTGAGTG CTGATGCACA AGTTGACAGG	960
CTGATTACAG GAAGACTTAC AGCACTTAAT GCATTTGTGT CTCAGACTTT AACCAAGACAA	1020
GCAGAGGTTA GGGCTAGCAG ACAGCTTGCT AAGACAAAGG TAAATGAATG CGTTAGGTCT	1080
CAATCTCAGA GATTTGGATT CTGTGGTAAT GGTACACATT TATTTCACT TGCAAATGCA	1140

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GCACCAAATG	GCATGATCIT	CTTCACACA	GTGCTATTAC	CAACAGCTTA	TGAAACCGTG	1200
ACGGCCTGGT	CAGGTATTTG	TGCATCAGAT	GGCGATCGTA	CTTTGGACT	TGTTGTTAAG	1260
GATGTCCAGT	TGACGCTGTT	TCGCAATCTA	GATGACAAAT	TCTATTGAC	TCCCAGAACT	1320
ATGTATCAGC	CTAGAGTTGC	AACTAGTTCT	GATTTGTTTC	AAATTGAAGG	ATGTGATGTG	1380
TTGTTTGTAA	ATGCCACTGT	A				1401

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 250 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Met	Ile	Val	Leu	Val	Thr	Cys	Leu	Leu	Phe	Ser	Tyr	Asn	Ser	Val	Ile	
1						5			10						15	
Cys	Thr	Ser	Asn	Asn	Asp	Cys	Val	Gln	Val	Asn	Val	Thr	Gln	Leu	Pro	
						20		25						30		
Gly	Asn	Glu	Asn	Ile	Ile	Lys	Asp	Phe	Leu	Phe	His	Thr	Phe	Lys	Glu	
				35		40								45		
Glu	Gly	Ser	Val	Val	Val	Gly	Gly	Tyr	Tyr	Pro	Thr	Glu	Val	Trp	Tyr	
				50		55								60		
Asn	Cys	Ser	Arg	Ser	Ala	Thr	Thr	Ala	Tyr	Lys	Asp	Phe	Ser	Asn		
					65	70		75						80		
Ile	His	Ala	Phe	Tyr	Phe	Asp	Met	Glu	Ala	Met	Glu	Asn	Ser	Thr	Gly	
				85		90								95		
Asn	Ala	Arg	Gly	Lys	Pro	Leu	Leu	Val	His	Val	His	Gly	Asp	Pro	Val	
				100		105								110		
Ser	Ile	Ile	Ile	Tyr	Ile	Ser	Ala	Tyr	Arg	Asp	Asp	Val	Gln	Gly	Arg	
				115		120								125		
Pro	Leu	Leu	Lys	His	Gly	Leu	Leu	Cys	Ile	Thr	Lys	Asn	Lys	Ile	Ile	
				130		135								140		
Asp	Tyr	Asn	Thr	Phe	Thr	Ser	Ala	Gln	Trp	Ser	Ala	Ile	Cys	Leu	Gly	
				145		150								160		
Asp	Asp	Arg	Lys	Ile	Pro	Phe	Ser	Val	Ile	Pro	Thr	Gly	Asn	Gly	Thr	
				165		170								175		
Lys	Ile	Phe	Gly	Leu	Glu	Trp	Asn	Asp	Asp	Tyr	Val	Thr	Ala	Tyr	Ile	
				180		185								190		
Ser	Asp	Arg	Ser	His	His	Leu	Asn	Ile	Asn	Asn	Trp	Phe	Asn	Asn		
				195		200								205		
Val	Thr	Ile	Leu	Tyr	Ser	Arg	Ser	Ser	Thr	Ala	Thr	Trp	Gln	Lys	Ser	
				210		215								220		

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Ala Ala Tyr Val Tyr Gln Gly Val Ser Asn Phe Thr Tyr Tyr Lys Leu
225 230 235 240

Asn Asn Thr Asn Gly Leu Lys Ser Tyr Glu
245 250

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 201 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Ser Phe Asn Leu Thr Thr Gly Asp Ser Gly Ala Phe Trp Thr Ile Ala
1 5 10 15

Tyr Thr Ser Tyr Thr Asp Ala Leu Val Gln Val Glu Asn Thr Ala Ile
20 25 30

Lys Lys Val Thr Tyr Cys Asn Ser His Ile Asn Asn Ile Lys Cys Ser
35 40 45

Gln Leu Thr Ala Asn Leu Gln Asn Gly Phe Tyr Pro Val Ala Ser Ser
50 55 60

Glu Val Gly Leu Val Asn Lys Ser Val Val Leu Leu Pro Ser Phe Tyr
65 70 75 80

Ser His Thr Ser Val Asn Ile Thr Ile Asp Leu Gly Met Lys Arg Ser
85 90 95

Gly Tyr Gly Gln Pro Ile Ala Ser Thr Leu Ser Asn Ile Thr Leu Pro
100 105 110

Met Gln Asp Asn Asn Thr Asp Val Tyr Cys Ile Arg Ser Asn Gln Phe
115 120 125

Ser Val Tyr Val His Ser Thr Cys Lys Ser Ser Leu Trp Asp Asp Val
130 135 140

Phe Asn Ser Asp Cys Thr Asp Val Leu Tyr Ala Thr Ala Val Ile Lys
145 150 155 160

Thr Gly Thr Cys Pro Phe Ser Phe Asp Lys Leu Asn Asn Tyr Leu Thr
165 170 175

Phe Asn Lys Phe Cys Leu Ser Leu Asn Pro Val Gly Ala Asn Cys Lys
180 185 190

Phe Asp Val Ala Ala Arg Thr Arg Thr
195 200

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 251 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: unknown

80

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Glu Asn Met Glu Ile Asp Ser Met Leu Phe Val Ser Glu Asn Ala Leu
1 5 10 15

Lys Leu Ala Ser Val Glu Ala Phe Asn Ser Thr Glu Thr Leu Asp Pro
20 25 30

Ile Tyr Lys Glu Trp Pro Asn Ile Gly Gly Ser Trp Leu Gly Gly Leu
35 40 45

Lys Asp Ile Leu Pro Ser His Asn Ser Lys Arg Lys Tyr Arg Ser Ala
50 55 60

Ile Glu Asp Leu Leu Phe Asp Lys Val Val Thr Ser Gly Leu Gly Thr
65 70 75 80

Val Asp Glu Asp Tyr Lys Arg Cys Thr Gly Gly Tyr Asp Ile Ala Asp
85 90 95

Leu Val Cys Ala Gln Tyr Tyr Asn Gly Ile Met Val Leu Pro Gly Val
100 105 110

Ala Asn Asp Asp Lys Met Ala Met Tyr Thr Ala Ser Leu Ala Gly Gly
115 120 125

Ile Thr Leu Gly Ala Leu Gly Gly Ala Val Ser Ile Pro Phe Ala
130 135 140

Ile Ala Val Gln Ala Arg Leu Asn Tyr Val Ala Leu Gln Thr Asp Val
145 150 155 160

Leu Ser Lys Asn Gln Gln Ile Leu Ala Asn Ala Phe Asn Gln Ala Ile
165 170 175

Gly Asn Ile Thr Gln Ala Phe Gly Lys Val Asn Asp Ala Ile His Gln
180 185 190

Thr Ser Gln Gly Leu Ala Thr Val Ala Lys Ala Leu Ala Lys Val Gln
195 200 205

Asp Val Val Asn Thr Gln Gly Gln Ala Leu Ser His Leu Thr Val Gln
210 215 220

Leu Gln Asn Asn Phe Gln Ala Ile Ser Ser Ser Ile Ser Asp Ile Tyr
225 230 235 240

Asn Arg Leu Asp Glu Leu Ser Ala Asp Ala Gln
245 250

What is claimed is:

1. An isolated protein sequence comprising a selected sequence from the S protein of a canine coronavirus strain, optionally fused to a second selected fusion protein.
2. The protein according to claim 1 wherein said strain is CCV 1-71.
3. The protein according to claim 1 comprising amino acid residues 1 to 1452 SEQ ID NO: 2.
4. The protein according to claim 1 wherein said selected sequence is selected from the group consisting of: 1113-1236 SEQ ID NO:25, 540-599 SEQ ID NO:27, 342-388 SEQ ID NO:29, 137-153 SEQ ID NO:31, 375-388 SEQ ID NO:33, 1424-1440 SEQ ID NO:35, 1407-1420 SEQ ID NO:37, 1342-1406 SEQ ID NO:39, 398-652 SEQ ID NO:44, 128-555 SEQ ID NO:43, and 447-628 SEQ ID NO:45.
5. An isolated DNA sequence comprising a selected nucleotide sequence from the S gene of a canine coronavirus strain, optionally associated with the nucleotide sequence encoding a fusion protein.
6. The DNA sequence according to claim 5 wherein said selected sequence comprises nucleotides 1 to 4356 SEQ ID NO: 1.
7. The DNA sequence according to claim 5 wherein the selected sequence is a nucleotide sequence selected from the group consisting of: 3337-3708 SEQ ID NO:24, 1618-1797 SEQ ID NO:26, 1024-1164 SEQ ID NO:28, 409-459 SEQ ID NO:30, 1123-1164 SEQ ID NO:32, 4270-4320 SEQ ID NO:34,

4219-4260 SEQ ID NO:34, 4024-4218 SEQ ID NO:38, 1192-1956 SEQ ID NO:40, 382-1665 SEQ ID NO:42, and 1339-1884 SEQ ID NO:44.

8. A method for the production of a recombinant CCV protein comprising culturing a selected host transformed with a DNA sequence encoding a selected CCV S protein or fragment thereof in operative association with regulatory sequences capable of regulating the expression of said protein.

9. The method according to claim 8 wherein said host is a mammalian cell.

10. The method according to claim 8 wherein said host is a viral vector.

11. A recombinant DNA molecule comprising a DNA sequence coding for a selected portion of a canine coronavirus S protein, said DNA sequences in operative association with regulatory sequences capable of directing the expression thereof in host cells.

12. A vaccine composition comprising an effective amount of a canine coronavirus protein comprising a selected canine coronavirus strain S protein, or immunogenic fragment thereof and an optional carrier.

13. A composition according to claim 12 wherein said strain is CCV 1-71.

14. The composition according to claim 12 wherein said S protein is a fusion protein.

15. The vaccine composition according to claim 12 further comprising an immunogenic amount of one or more additional antigens.

16. A method for vaccinating an animal against CCV gastroenteritis which comprises the step of internally administering to the animal an effective amount of a CCV S protein, S fusion protein or an immunogenic fragment thereof.

17. An antibody to a protein comprising a selected sequence from the S gene of a canine coronavirus strain, said antibody being specific for a CCV S gene epitope.

18. The protein according to claim 17 wherein said strain is CCV 1-71.

19. A diagnostic reagent comprising a selected sequence from the S protein of a canine coronavirus strain, optionally fused to a second selected fusion protein, said sequence optionally associated with a detectable label.

20. A diagnostic reagent comprising an antibody to a protein comprising a selected sequence from the S gene of a canine coronavirus strain, said antibody being specific for a CCV S gene epitope and said antibody optionally associated with a detectable label.

21. A diagnostic reagent which comprises a nucleotide sequence encoding or flanking a CCV S protein or fragment, said nucleotide sequence optionally associated with a detectable label.

22. A diagnostic kit comprising one or more diagnostic reagents selected from the group consisting of

(a) a selected sequence from the S protein of a canine coronavirus strain, optionally fused to a second selected fusion protein, said sequence optionally associated with a detectable label;

(b) an antibody to a protein comprising a selected sequence from the S gene of a canine coronavirus strain, said antibody being specific for a CCV S gene epitope and said antibody optionally associated with a detectable label; and

(c) a nucleotide sequence encoding or flanking a CCV S protein or fragment, said nucleotide sequence optionally associated with a detectable label.

23. A method of diagnosing ccv infection in dogs comprising treating a tissue sample from a dog with a diagnostic reagent of claim 22.

24. The method according to claim 23 wherein dogs previously exposed to ccv or to a ccv vaccine are detected.

25. The method according to claim 23 wherein said diagnostic method can differentiate exposure to ccv from exposure to another related coronavirus.

26. The method according to claim 23 wherein said diagnostic method can differentiate exposure to different strains of ccv.

27. The method according to claim 23 wherein said method can identify dogs at advanced stages of ccv infection.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/04692

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
 US CL :530/350, 409, 387.1; 424/89; 536/27; 435/5, 6, 69.3, 320.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 409, 387.1; 424/89; 536/27; 435/5, 6, 69.3, 320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A, 0,264,979 (de Groot et al) 27 April 1988, see entire document.	1-27
Y	EP, A, 0,278,541 (Jacobs et al) 17 August 1988, see entire document.	1-27
Y	Proceedings of the National Academy of Sciences USA, Volume 80, issued March 1983, R. A. Young et al., "Efficient Isolation of Genes by Using Antibody Probes", pp. 1194-1198, see entire document.	1-27
Y	US, A, 4,904,468 (Gill et al) 27 February 1990, see entire document.	1-27

Further documents are listed in the continuation of Box C. See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 JULY 1993

Date of mailing of the international search report

03 AUG 1993

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

D. BARND

Facsimile No. NOT APPLICABLE

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/04692

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of General Virology, Volume 71, issued 1990, T. Raabe et al., "Nucleotide Sequence of the Gene Encoding the Spike Glycoprotein of Human Coronavirus HCV 229E", pp. 1065-1073, see Figure 4.	1-27
Y	Archives of Virology, Volume 117, issued 1991, T. Hohdatsu et al., "Characterization of Monoclonal Antibodies Against Feline Infectious Peritonitis Virus Type II and Antigenic Relationship Between Feline, Porcine, and Canine Coronaviruses", pp. 85-95, see entire document.	1-27
Y	EP, A, 0,376,744 (Dale et al) 04 July 1990, see entire document.	17-27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/04692

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (5):

C07K 3/00, 15/00, 13/00; A61K 39/12; C07H 15/12; C12N 15/00; C12P 21/06; C12Q 1/70, 1/68

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

EMBL, GenBank, SwissProt, PIR, GeneSeq, Medline, CA, Biosis, WPI, APS
search terms: coronavirus, pcplomer, S protein, vaccin?, antibod?, diagnos?

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